THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

Investigations into the bone health of men on the prostate cancer continuum: A focus on osteoporosis and health behaviours

Annie-Claude Marie Lassemillante

Master of Dietetics Studies (The University of Queensland)

Bachelor of Applied Science (Nutrition and Food) (University of Western Sydney)

A thesis submitted for the degree of Doctor of Philosophy at

The University of Queensland in 2015

School of Human Movement and Nutrition Sciences

Mater Research - UQ

Abstract

Prostate cancer is highly prevalent in Australia, with 17 050 cases in 2014. A common treatment for this disease is androgen deprivation therapy (ADT), or castration, which has significant side-effects hence increasing morbidity in this patient population. These side-effects include gynecomastia, erectile dysfunction, fatigue, metabolic syndrome, and severe bone loss. The latter is well documented with 1.5% to 4.0% of bone loss within 12 months of treatment initiation. This leads to osteoporosis (porous bones), which increases the risks of fractures. Some clinical guidelines recommend bone health monitoring and interventions when ADT is prescribed to the prostate cancer patient, but evidence suggests that these practices are not well implemented by the treating team. For example, lifestyle factors such as increasing calcium and vitamin D intake are not routinely recommended to men with prostate cancer on ADT as part of standard practice. There is also little evidence on the bone health of men with prostate cancer before castration, which demonstrates the lack of research attention given to osteoporosis in men and preventative strategies to minimise adverse events later on the prostate cancer continuum. This research program therefore aims to increase the understanding of bone health in men on the prostate cancer continuum, regardless of treatment.

The findings from three studies demonstrate the burden of poor bone health and lack of interventions in men with prostate cancer and prostate cancer survivors. First, the evidence on the prevalence of osteoporosis in men with prostate cancer was summarised in two meta-analyses, where it was found that (i) men with prostate cancer experience poor bone health before treatment with ADT, with 4% to 38% having osteoporosis, and (ii) the prevalence of osteoporosis in men with prostate cancer on ADT varies between 9% and 53% with this variation partially explained by treatment duration, disease stage, ethnicity, and site of osteoporosis measurement. Secondly, data from the Dubbo Osteoporosis Epidemiology Study were analysed to estimate the incidence of poor bone health and fractures in men on the prostate cancer continuum. The incidence of osteoporosis after diagnosis of prostatic disease was 20.8% in men with benign prostatic hyperplasia, 23.1% in hormone-naïve men with prostate cancer, and 44.4% in men with prostate cancer on ADT. Post-diagnostic fractures were present in 18.4% of men with benign prostatic hyperplasia, 36.3% of hormone-naïve men with prostate cancer, and 48.0% of men with prostate cancer on ADT. In light of the significant osteoporosis problem in men with prostate cancer, a pilot cross-sectional study was conducted to identify (i) the

bone health related health behaviours that this population engage in, and (ii) the psycho-behavioural and psycho-social factors that drive such health behaviours. Dietary behaviours of a small group of men with prostate cancer and survivors were analysed and described in detail using an innovative approach. This dietary analysis method involved grouping food intake into specific food categories, which were based on the food categories reported in the National Nutrition and Physical Activity Survey. The results from this analysis were also compared with the food intake of Australian men from the Australian health Survey to identify typical or atypical dietary behaviours. It was found that men with prostate cancer generally have healthier eating behaviours than an age-matched sample of men from the Australian Health Survey. Men with prostate cancer did not meet their calcium requirements (average daily intake including supplements was 870 mg versus Recommended Daily Intake 1000 - 1200 mg/day) as they did not consume enough dairy products, revealing a problem since over 70% of the study participants had poor bone health. The next stage of this study involved measuring the extent of osteoporosis knowledge, perceived health beliefs, and self-efficacy with bone healthy behaviours in men with prostate cancer and survivors. Three questionnaires were used to measure these psycho-behavioural and psycho-social factors. Participants had inadequate osteoporosis knowledge with a mean score of 43.3% (SD 18%) on the Facts on Osteoporosis Quiz (adequate knowledge defined as a score exceeding 80%). Participants scored low on the subscale measuring barriers to exercise (median = 11; IQR 6.5), indicating minimal barriers to exercise participation, and the subscale measuring the benefits of exercise scored the highest (median = 24; IQR 3.5) compared with the other subscales. Men with prostate cancer and survivors were highly confident in their exercise and calcium self-efficacy (83.0%, IQR 24.0% and 85.7%, IQR 27.0% respectively). Unfortunately this confidence did not transfer to specific dietary behaviours as they did not meet their calcium or dairy intake requirements.

This thesis supports the extent of the osteoporosis problem in men with prostate cancer and outlines the gap in clinical practice, which translates into poor bone health management strategies among prostate cancer patients. More studies are therefore warranted, and the interventions need to (i) be based on health behaviour theoretical frameworks, (ii) use a multidisciplinary approach, (iii) include men early on the prostate cancer continuum as well as survivors, (iv) use tools targeted at a male audience, and (v) provide practical information such as specific strategies on how to increase the calcium

content of a meal. Since nutrition research needs to grow in this area, Dietitians will benefit from collaborating with exercise physiologists, who seem more active in this research area, in investigating a nutrition-exercise intervention for osteoporosis management in men with prostate cancer and survivors. There is a need to update the clinical guidelines for the clinical treatment of prostate cancer, in order to incorporate recommendations for bone health management and the importance of a multidisciplinary approach in doing so.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

I acknowledge that an electronic copy of my thesis must be lodged with the University Library and, subject to the policy and procedures of The University of Queensland, the thesis be made available for research and study in accordance with the Copyright Act 1968 unless a period of embargo has been approved by the Dean of the Graduate School.

I acknowledge that copyright of all material contained in my thesis resides with the copyright holder(s) of that material. Where appropriate I have obtained copyright permission from the copyright holder to reproduce material in this thesis.

Publications during candidature

Publications

Wright OR, Bauer JD, Lassemillante A-CM. Nutrition and Prostate Cancer: Latest Insights and Practice Recommendations. Cancer Forum. 2011;35(2):107-11.

Lassemillante A-CM, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors: a meta-analysis. Endocrine. 2014;45(3):370-81.

Lassemillante AC, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors II: a meta-analysis of men not on androgen deprivation therapy. Endocrine. 2015.

Lassemillante A-CM, Center JR, Eisman JA, Nguyen TV, Hooper JD, Prins J, Wright OL. Bone health of men with benign prostatic hyperplasia and prostate cancer: secondary analysis of the Dubbo Osteoporosis Epidemiology Study. (under-review).

Lassemillante A-CM, Skinner TL, Hooper JD, Prins JB, Wright ORL Osteoporosis-related health behaviors in men with prostate cancer and survivors: Exploring osteoporosis knowledge, health beliefs and self-efficacy. American Journal of Men's Health (Accepted, corrected proof).

Lassemillante AC, Skinner TL, Hooper JD, Prins JB, Wright ORL. Maximising the richness of dietary data: a pilot study of the dietary intake of men with prostate cancer and prostate cancer survivors. (under-review)

Conference presentations and posters

May 2015

Dietitians Association of Australia 32nd National Conference

Lassemillante AC, Skinner TL, Hooper JD, Prins JB, Wright ORL. Food group analysis: using food groups from the National Nutrition and Physical Activity Survey to analyse food intake. Nutrition & Dietetics. 2015;72:2.

August 2014

Faculty of Health and Behavioural Sciences 3-Minute Thesis competition – Runner-up

May 2014

Dietitians Association of Australia 31st National Conference – Won First Conference Presenter Award.

Lassemillante A-C, Hooper J, Prins J, Doi S, Wright O. Osteoporosis in prostate cancer patients not on androgen deprivation therapy: A meta-analysis. Nutrition & Dietetics. 2014;71:2-32.

August 2013

Moderated poster at the Prostate Cancer World Congress & 14th Australasian Prostate Cancer Conference.

Lassemillante A-C, Hooper J, Prins J, Doi S, Wright O. The prevalence of osteoporosis in men with prostate cancer on androgen deprivation therapy: a systematic review and meta-analysis. BJU Int. 2013;112:35.

April 2013

School of Human Movement and Nutrition Sciences Postgraduate Conference.

November 2012

Joint Meeting IPOS 14th World Congress and Clinical Oncological Society of Australia 39th Annual Scientific Meeting.

Lassemillante A. C. M., Wright O. R. L, Nguyen D. N., Eisman J. A., Center J. R., Nguyen TV, et al. The effect of prostate cancer not treated with ADT, on bone mineral density: The Dubbo Osteoporosis Epidemiology Study. Asia Pac J Clin Oncol. 2012;8.

Publications included in this thesis

Lassemillante A-CM, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors: a meta-analysis. Endocrine. 2014;45(3):370-81 – incorporated in Chapter 1

Contributor	**Statement of contribution**
Annie-Claude M. Lassemillante (Candidate)	Literature search (100%) Review and critical appraisal of articles (100%) Ran meta-analysis (20%) Wrote the paper (70%)
Suhail A. R. Doi	Ran meta-analysis (80%) Wrote and edited paper (40%)
John D. Hooper	Reviewed and edited paper (30%)
John B. Prins	Reviewed and edited paper (10%)
Olivia R. L. Wright	Reviewed and edited paper (50%)

Lassemillante AC, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors II: a meta-analysis of men not on androgen deprivation therapy. Endocrine. 2015 – incorporated in Chapter 1

Contributor	**Statement of contribution**
Annie-Claude M. Lassemillante (Candidate)	Literature search (100%) Review and critical appraisal of articles (100%) Ran meta-analysis (20%) Wrote the paper (70%)
Suhail A. R. Doi	Ran meta-analysis (80%) Wrote and edited paper (40%)
John D. Hooper	Reviewed and edited paper (30%)
John B. Prins	Reviewed and edited paper (10%)
Olivia R. L. Wright	Reviewed and edited paper (50%)

Lassemillante A-CM, Center JR, Eisman JA, Nguyen TV, Hooper JD, Prins J, Wright OL. Bone health of men with benign prostatic hyperplasia and prostate cancer: secondary analysis of the Dubbo Osteoporosis Epidemiology Study. (under-review) – incorporated in Chapter 2

Contributor	**Statement of contribution**
Annie-Claude M. Lassemillante (Candidate)	Conceptualisation of research question (80%) Analysed the data (95%) Wrote the paper (100%)
Jacqueline D. Center	Data collection, management, and ownership (100%) Reviewed and edited the paper (5%)
John Eisman	Data collection, management, and ownership (100%)
Tuan Nguyen	Data collection, management, and ownership (100%)
John D. Hooper	Reviewed and edited paper (10%)
John B. Prins	Reviewed and edited paper (5%)
Olivia R. L. Wright	Reviewed and edited paper (50%)

Lassemillante A-CM, Skinner TL, Hooper JD, Prins JB, Wright ORL Osteoporosis-related health behaviors in men with prostate cancer and survivors: Exploring osteoporosis knowledge, health beliefs and self-efficacy. American Journal of Men's Health (accepted, corrected proof) – incorporated in Chapter 3

Contributor	**Statement of contribution**
Annie-Claude M. Lassemillante (Candidate)	Study design (90%) Data collection (100%) Data entry (100%) Analysed the data (95%) Wrote the paper (100%)
John D. Hooper	Reviewed and edited paper (25%)
John B. Prins	Reviewed and edited paper (5%)
Tina Skinner	Study design (10%) Participant recruitment (50%) Reviewed and edited paper (50%)
Olivia R. L. Wright	Study design (10%) Reviewed and edited paper (50%)

Lassemillante AC, Skinner TL, Hooper JD, Prins JB, Wright ORL. Maximising the richness of dietary data: a pilot study of the dietary intake of men with prostate cancer and prostate cancer survivors. (under-review)

Contributor	**Statement of contribution**
Annie-Claude M. Lassemillante (Candidate)	Study design (90%) Data collection (95%) Data entry (95%) Conceptualisation of analysis (95%) Analysed the data (95%) Wrote the paper (100%)
Stephanie Hsu	Data collection (5%) Data entry (5%) Conceptualisation of analysis (5%)
John D. Hooper	Reviewed and edited paper (25%)
John B. Prins	Reviewed and edited paper (5%)
Tina Skinner	Study design (10%) Participant recruitment (50%) Reviewed and edited paper (50%)
Olivia R. L. Wright	Study design (10%) Reviewed and edited paper (50%)

Contributions by others to the thesis

Dr Olivia Wright, Associate Professor John Hooper, and Professor John Hooper contributed significantly to the conception and design of each study, to the interpretation of results, and critically reviewing the manuscripts, conference abstract and this thesis.

Professor Suhail Doi provided specialist training to the candidate on meta-analyses and contributed significantly to both meta-analyses published in *Endocrine*.

Associate Professor Jaqueline Center, Professor John Eisman, and Professor Tuan Nguyen are the lead investigators on the Dubbo Osteoporosis Epidemiology Study. They collected, and managed the data used in CHAPTER 2. Mrs Denia Mang provided administrative support in accessing these data. Dr Enamul Kabir provided statistical assistance in conducting the secondary analysis of the Dubbo Osteoporosis Epidemiology Study.

Dr Tina Skinner, from the School of Human Movement and Nutrition Sciences, is the lead investigator in the student-led exercise clinic from which study participants were recruited for the pilot cross-sectional study presented in CHAPTER 3.

Professor Sandra Capra was consulted for her expertise in dietary analysis methodology, which assisted in the development of the food group analysis methodology used in this thesis.

Miss Stephanie Hsu was a Master of Dietetics Studies, who assisted in dietary data collection and entry as part of a research project.

Statement of parts of the thesis submitted to qualify for the award of another degree

None

Acknowledgements

I would like to extend my deepest gratitude and most sincere thank you to all who accompanied me along this PhD journey. I would like to thank the following people for making this thesis possible:

First of all I would to thank my principal advisor Dr Olivia Wright. She has been my mentor and greatest supporter throughout this journey. She has provided me with ongoing guidance and feedback while giving me room to grow as a researcher. I appreciate all her contributions of ideas, time, and funding that have benefited to the completion of my PhD.

I would like to thank Associate Professor John Hooper for his belief in me and unconditional support. His feedback and insight during this PhD have been invaluable. Thank you also to Professor John Prins for inspiring me to be the best I can be. I am humbled to have had the opportunity to learn from his wealth of knowledge and expertise. I will always carry with me this notion that he taught me: “we do research to help people”.

Thank you to all my collaborators Dr Tina Skinner, A/Prof Jacqueline Center, and Professor Suhail Doi, who gave me faith in working together for the advancement of scholarship.

I am thankful to have such supportive friends, most importantly Rebecca Dickinson, who has ridden the highs and lows of this PhD with me. My biggest gratitude goes to my husband, without whose support, love, and sacrifice I would not have completed this PhD. Thank you to my family for a lifetime of support and respect for the path that I have chosen in life. I will be forever indebted to my parents who have sacrificed so much for me to achieve my ambitions. Thank you.

Finally I dedicate this PhD and thesis to Mr Max Lassémillante, my grand-father and greatest inspiration in life. I have achieved what he was denied because of the war.

Keywords

Androgen deprivation therapy, bone health, diet, food analysis, food groups, health beliefs. knowledge, osteoporosis, prostatic neoplasm, self-efficacy.

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 111199, Nutrition and Dietetics not elsewhere specified, 50%

ANZSRC code: 111299, Oncology and Carcinogenesis not elsewhere specified, 25%

ANZSRC code: 110322, Rheumatology and Arthritis, 25%

Fields of Research (FoR) Classification

FoR code: 1111, Nutrition and Dietetics, 50%

FoR code: 1112, Oncology and Carcinogenesis, 25%

FoR code: 1103, Clinical Sciences, 25%

Contents

List of Tables

List of Figures

List of abbreviations used

ADG, Australian Dietary Guidelines

ADT, Androgen Deprivation Therapy

AHS, Australian Health Survey

ALP, Alkaline phosphatase

BMD, Bone mineral density

BMI, Body mass index

BMR, Basal metabolic rate

BPH, Benign prostatic hyperplasia

CAB, Combination androgen blockade

CTx, C-terminal telopeptide of type 1 collagen

DHT, Dihydrotestosterone

DOES, Dubbo osteoporosis epidemiology study

DXA, Dual x-ray absorptiometry

EAU, European association of urology

EI, Energy intake

FN, Femoral neck

FOOQ, Facts on Osteoporosis Quiz

FSH, Follicle-stimulating hormone

GnRH, Gonadotropin-releasing hormone

HBM, Health belief model

IQR, Inter-quartile range

ISCD, International Society for Clinical Densitometry

IU, International units

LS, Lumbar spine

MOKQ, Men's Osteoporosis Knowledge Quiz

NCCN, National Comprehensive Cancer Network

NH&MRC, National Health and Medical Research Council

NHANES, National Health and Nutrition Examination Survey

NICE, National Institute for Health and Care Excellence

NNPAS, National Nutrition and Physical Activity Survey

OC, Osteocalcin

OHBS, Osteoporosis Health Belief Scale

OPG, Osteoprotegerin

OSES, Osteoporosis Self-Efficacy Scale

P1NP, Procollagen type 1 N propeptide

PSA, Prostate specific antigen

RANK, Receptor activator of nuclear factor κ B

RANKL, Receptor activator of nuclear factor κ B ligand

RDA, Recommended dietary allowance

RDI, Recommended daily intake

ROB, Risk of bias

ROI, Region of interest

SD/s.d., Standard deviation

SHBG, Sex hormone-binding globulin

SPSS, Statistical Package for Social Sciences

UK, United Kingdom

USA, United States of America

WHO, World Health Organization

WHR, Waist-to-hip ratio

CHAPTER 1 BACKGROUND AND REVIEW OF THE LITERATURE

1.1 Introduction

Prostate cancer is one of the most frequently diagnosed cancers worldwide with Australia and New Zealand recording the highest incidence. Locally, prostate cancer is the most prevalent cancer (17 050 cases in 2014), apart from non-melanoma skin cancer, and is the second leading cause of male cancer deaths (3 390 deaths in 2014) (1). This thesis focuses on the bone health of men with prostate cancer and prostate cancer survivors. This includes the prevalence and incidence of poor bone health in men on the prostate cancer/health continuum, as well as health behaviours and drivers of these behaviours (self-efficacy, health beliefs, and knowledge).

The interplay between prostate cancer and bone health will be presented in a comprehensive review of the literature in the form of two meta-analyses. This is followed by a review of the clinical guidelines for prostate cancer, to identify the current evidence-based recommendations on the bone health management in this patient group. CHAPTER 2 presents the findings from the secondary analysis of one of the biggest longitudinal Australian study on osteoporosis (from the Dubbo Osteoporosis Epidemiology Study [DOES] database). This chapter presents the state of bone health in men with prostate cancer and benign prostatic hyperplasia (BPH). The results from the cross-sectional study presented in CHAPTER 3 address the role of health behaviours and their psychological determinants within the context of bone health in the prostate cancer patient. CHAPTER 4 presents a comprehensive discussion and consideration of implications for future research. Figure 1.1 depicts the framework used to guide reporting throughout this thesis. Relevant parts of this diagram will be highlighted at the beginning of chapters/sections addressing such parts. The introduction of this thesis will address each part separately (implications of prostate cancer for bone health, osteoporosis, followed by health behaviours and their psychological determinants). The conclusion of this thesis presented in CHAPTER 4 integrates the discussion of how the different parts of the framework in Figure 1.1 are interrelated.

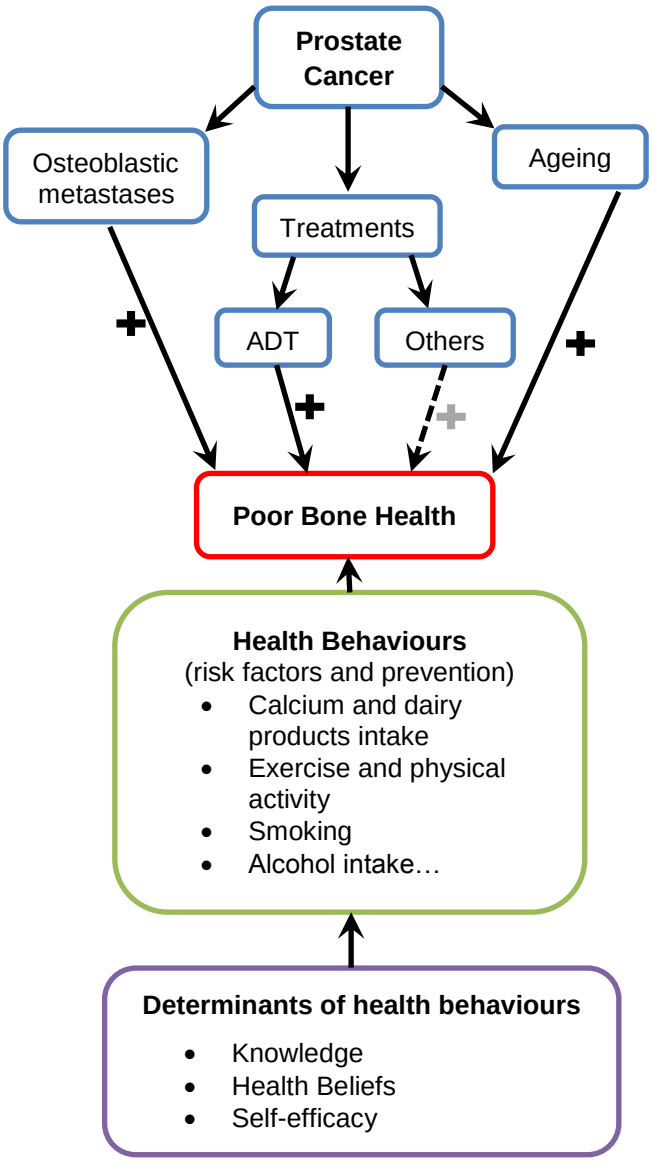


Figure 1.1 Summary of the relationship between prostate cancer, poor bone health, and health behaviours and their determinants.[1]

[1]**Notes:** ADT, androgen deprivation therapy; dotted line represent a positive (plus sign in grey) weak association supported by some evidence.

The prostate cancer continuum is mentioned throughout this thesis and refers to different stages of prostate cancer and prostate health, all of which have different co-morbidities associated with treatment or lack thereof:

- BPH is at the beginning of this continuum even though it does not lead to prostate cancer (2). The presenting symptoms of this benign prostatic disease often drive patients to seek medical attention, which leads to testing (including digital rectal examination and prostate-specific antigen [PSA] screening) to rule out prostate

cancer. Therefore it is a clinically relevant disease on the prostate cancer continuum that shares commonalities with prostate cancer (elevated PSA) (2) and has been used as a comparative group in many prostate cancer research studies. Men with BPH are likely to have age-related co-morbidities but none associated with prostate cancer treatment.

- Prostate cancer not treated with androgen deprivation therapy (ADT) is next on the continuum based on the assumption that the disease is not advanced enough to require androgen ablation. Men with castrate resistant prostate cancer previously treated with (and no longer on) ADT are not included here or on this continuum. Hormone-naïve men with prostate cancer are likely to have cancer-related and/or cancer treatment-related adverse effects, as well as similar age-related co-morbidities as men with BPH.

- Prostate cancer treated with ADT is the third point on this continuum as this group needs to meet worse disease parameters to qualify for this treatment (3). Men on this point of the continuum are likely to have (i) ADT-related adverse effects, (ii) similar age-related co-morbidities as men with BPH, and (iii) co-morbidities experienced by men with prostate cancer not on ADT. The iatrogenic effects of ADT are significant and are discussed in section 1.2.

- At the end of this continuum are prostate cancer survivors, who are free from prostate cancer and have undergone different types of treatment, including ADT. The men in this group may present with different co-morbidities, which can be due to different treatment modalities, but for the purpose of this thesis they have been grouped because of recruitment challenges.

1.2 Implications of prostate cancer for bone health

A feature of prostate cancer is its propensity to metastasise to bone as demonstrated by the identification of skeletal involvement at autopsy of up to 90% of prostate cancer patients with metastases (4, 5). Bone provides an ideal environment (a niche) for prostate cancer cells as demonstrated by the “seed-and-soil” theory by Stephan Paget (6). Prostate cancer cells generally niche to the axial bone and long bones where there is an increased

marrow cellularity as well as increased active bone remodelling (discussed in section 1.3.1) (7, 8). Bone resorption and formation are both increased in prostate cancer metastasis as demonstrated by elevation of their respective biomarkers (9) but as the disease progresses bone formation predominates (10). This is indicated by an increase in osteoid surface area, osteoid volume, and bone mineral apposition rate (11). Moreover, one of the receptors involved in normal osteoclastogenesis (formation of bone resorbing cells), osteoprotegerin, has been found to be elevated among prostate cancer patients (12-15), thus indicating a disruption in bone homeostasis where osteoclastic bone resorption is reduced.

The skeletal metastases are characteristically ‘blastic’ (osteo-dense), with increased local bone density demonstrable on imaging and increased number of osteoblasts (bone-forming cells) adjacent to prostate cancer cells (16, 17). Despite the locally increased osteoblastic activity leading to increased bone mass at the metastatic site, the associated bone architecture is abnormal, with altered volumetric and strength characteristics (18). This complication adds to the morbidity and mortality of prostate cancer whereby 54% of patients with metastases may experience skeletal related events including pathological fractures, bone pain, and spinal cord compression (19).

Treatment options for prostate cancer vary depending on the stage and grade of the disease. Active surveillance involves no pharmacological or surgical intervention, and is recommended for men with low risk prostate cancer with a life expectancy of less than 20 years (3). Active surveillance involves closely monitoring the disease progression through 6-monthly PSA testing, yearly digital rectal examination, and repeat prostate biopsy if needed (3). This treatment, or perceived absence of treatment, is also associated with uncertainty in men with prostate cancer (20), despite active surveillance being safe (21, 22). During that time some men feel pressured, by themselves or their families, to initiate a treatment to combat the cancer (23).

If the disease progresses then other forms of treatment are initiated. Radical prostatectomy is recommended for men with localised disease and involves the removal of the prostate gland (3). Another treatment modality for localised or metastatic disease is radiation therapy, which is used alone or with ADT (for patients with high risk prostate cancer) (3). ADT is unique to this disease, and is commonly used to manage metastatic

prostate cancer (3). Because of the iatrogenic effects of ADT, this treatment needs to be weighed against the potential benefits, short-term and long-term side effects, and the impact on the patient's quality of life (3). According to a survey of the Pharmaceutical Benefits Schedule in Australia (conducted for the purpose of this thesis), about 43 350 claims for ADT were made in 2013-14 (see Figure 1.2), which is a considerable increase since 2003 (24). It is however important to note that patients may claim more than once in a year as they may have received multiple prescriptions of ADT during that time. (see Appendix I for detailed use of ADT in Australia).

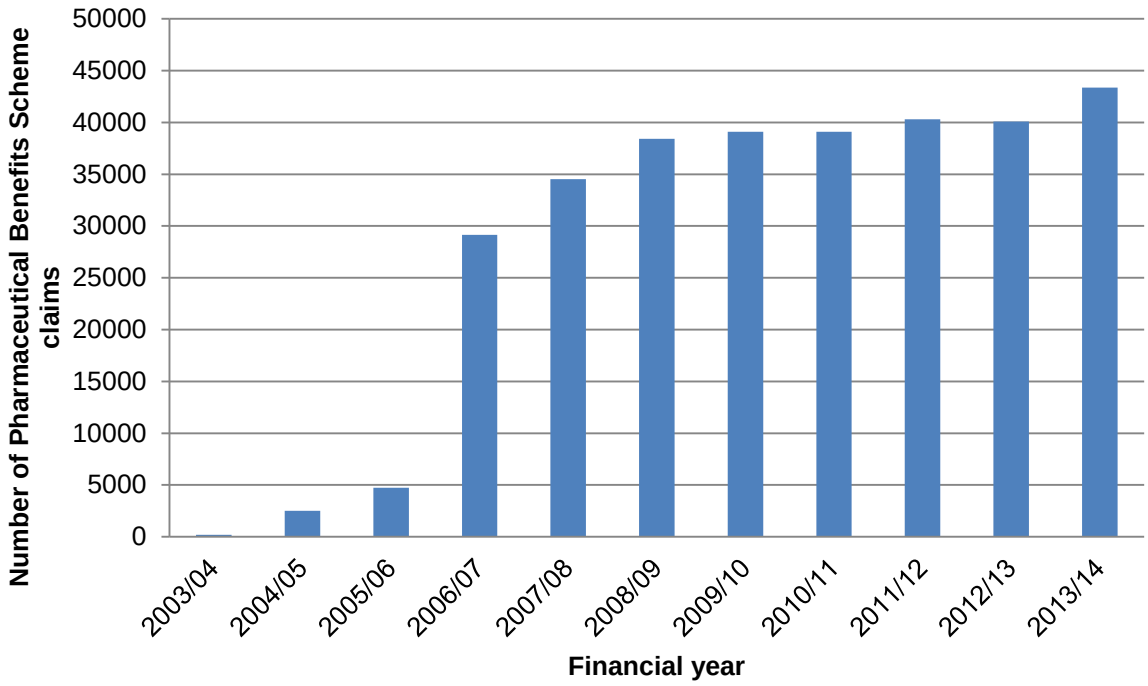


Figure 1.2 Summary of the Pharmaceutical Benefits Schedule statistics on the number of androgen deprivation therapy (Goserelin, Leuprolide Bicalutamide, and Degarelix) claims made since 2003.

Sources from (24).

ADT can be surgical, via bilateral orchiectomy, or pharmacological ((25); see Table 1.1). The former type of castration involves removal of the testes hence inhibiting the production of testosterone and oestradiol from the testicles (26). The other type of castration results in reduced production of testosterone or competitively binding with the androgen receptor inhibiting its activation (27). Under normal conditions oestrogen is produced from

aromatization of androgens (28); therefore during treatment with ADT, circulating oestrogen levels are low (29). Deficiencies in androgens and oestrogen are responsible for the side effects of ADT (30). Intermittent-ADT offers similar prostate cancer management outcomes as continuous ADT while impacting less on quality of life (31). This cyclical administration of ADT is based on PSA levels, where ADT is stopped when PSA levels are low and re-started when PSA rises to a predetermined level (no current consensus on the levels of PSA) (31).

Table 1.1 Common drugs used in pharmacological androgen deprivation therapy.

Drug class	Drugs	Mechanism of action	Side effects
Gonadotropin-releasing hormone (GnRH) agonists and antagonists	Leuprolide Goserelin Abarelix®	Luteinizing hormone receptor down-regulation to decrease luteinizing hormone, FSH and testosterone	Hot flashes Reduced lean bone mass Anaemia Osteoporosis Cardiovascular events
Adrenal ablating drugs	Ketoconazole		
Androgen receptor antagonists	Flutamide Bicalutamide Nilutamide	Binds to androgen receptor	Hot flashes Reduced lean body mass and energy Anaemia Osteoporosis Cardiovascular events
5-α-reductase inhibitor	Finasteride	Decreases conversion of testosterone to DHT	

FSH: follicle-stimulating hormone, DHT: dihydrotestosterone; Sourced from (27).

ADT leads to significant morbidity such as leading to Metabolic Syndrome (32), sexual dysfunction (33), gynecomastia, depression (34), and significant bone loss (35, 36) and muscle loss (37). The bone-specific side effects of ADT are mediated through deficiency of both androgens and oestrogen (38); where deficiency of the former reduces bone formation, and deficiency of the latter increases bone resorption (38). As a result net bone loss predominates during ADT, resulting in osteoporosis and low bone mass (39). Given the large economic burden of osteoporosis (40) and given the increasing number of men being treated with ADT, there is a need for more research in the prevention and management of osteoporosis in men with prostate cancer. There are many studies investigating and reporting on the effects of ADT on metabolic health, mental health, sexual health, and bone health. This thesis focusses on the latter, but also includes men not on ADT as they have not been as extensively studied.

1.3 Osteoporosis and bone biology

Osteoporosis is a common bone condition that affects older people, including both men and women (41). This disease is characterised by porous weak bones that break easily, and often goes undiagnosed due to the lack of symptoms (42, 43). Osteopenia, or low bone mass, is also a state of reduced bone density but not as severe as in osteoporosis ((44); see Table 1.2). Peak bone mass is generally attained in early adulthood, through bone mineral deposition in the skeleton since childhood (45). Bone maintenance is the next phase, where bone formation and bone resorption are in equilibrium. Menopause and old age, among other risk factors, are responsible for a disruption in this balance leading to net bone loss (46). Osteoporosis is a result of long term bone loss and its underlying mechanism has been explained in section 1.3.1.

Currently osteoporosis and osteopenia affect 4.72 million of Australians over 50 years of age, of which 22% have osteoporosis and the rest have osteopenia (40). This is a significant problem, as the number of Australian affected by poor bone health is estimated to increase to 6.2 million by 2022 (40). In 2012, it was estimated that 3.2% of men aged 50 years to 69 years and 12.9% of men aged over the age of 70 years were diagnosed with osteoporosis (40). The major clinical outcomes of poor bone health (osteoporosis and osteopenia) are osteoporotic fractures (47), which affected 140 822 Australians in 2012 (40). Osteoporosis and fractures are often associated with women but also affects men, with 30% of osteoporotic fractures, and associated costs, occurring in the latter group (40). A report by Osteoporosis Australia (40) found that the total direct and indirect cost of poor bone health and associated fractures was $2.75 billion in 2012 and will cost over $33.6 billion over the next 10 years.

Osteoporosis is diagnosed from bone mineral density (BMD), which is measured using dual X-ray absorptiometry (DXA) and compared with the average BMD of young males (44). This is expressed as the T-score, which is the number of standard deviations above or below the mean BMD of young adult males (44). Table 1.2 outlines the classification for the diagnosis of osteoporosis. The World Health Organization (WHO) recommends measuring BMD at the femoral neck (44), forearm, or lumbar spine when diagnosing osteoporosis (46). The latter region of interest (ROI) is a common site for osteoarthritis in men, which leads to the formation of osteophytes (48). These bone formations are dense

in nature, resulting in erroneously elevated BMD that is not representative of overall bone health; hence it may not be suitable to assess overall bone health in men (48).

Table 1.2 WHO densitometric classification for the diagnosis of osteoporosis.

Cut off value	Bone health status
T-score ≥ -1	Normal bone mass
-1 <T-score < -2.5	Low bone mass (formerly known as osteopenia)
T-score ≥ -2.5	Osteoporosis

Sourced from (47).

Osteoporosis and low bone mass (osteopenia) increase the risks of fragility fractures, but so do other risk factors (49). This is why low BMD alone cannot be used when assessing fracture risk. Fracture algorithms or risk assessment tools, more specifically the FRAX® algorithm has been validated and endorsed by the WHO for fracture risk assessment (50). Such tool takes into account BMD, and other risk factors, for example, previous fractures, body mass index (BMI), family history of fractures, smoking status, and glucocorticoid use (51). The FRAX® algorithm calculates the 10-year probability of major fractures (including hip fractures and other fractures) and hip fractures only (52). This tool has been used to identify patients needing pharmacological interventions for osteoporosis (53). For men over the age of 60, pharmacological intervention for osteoporosis is recommended for a 10-year probability of major fractures exceeding 20% threshold (54) (see Appendix II for an example of FRAX® algorithm)

1.3.1 **Bone biology explained**

In order to understand the interplay between bone health and disease, such as prostate cancer, it is important to understand bone biology. The integrity of bones is maintained through the process of bone remodelling. It involves the coupling of bone formation and resorption. These respective functions are carried out by osteoblasts, the bone forming cells; and osteoclasts, the bone resorbing cells (55). In adulthood bone remodelling is essential to repair micro-damage to the skeleton and for calcium homeostasis (56). Figure 1.3 summarises the main processes involved in bone remodelling.

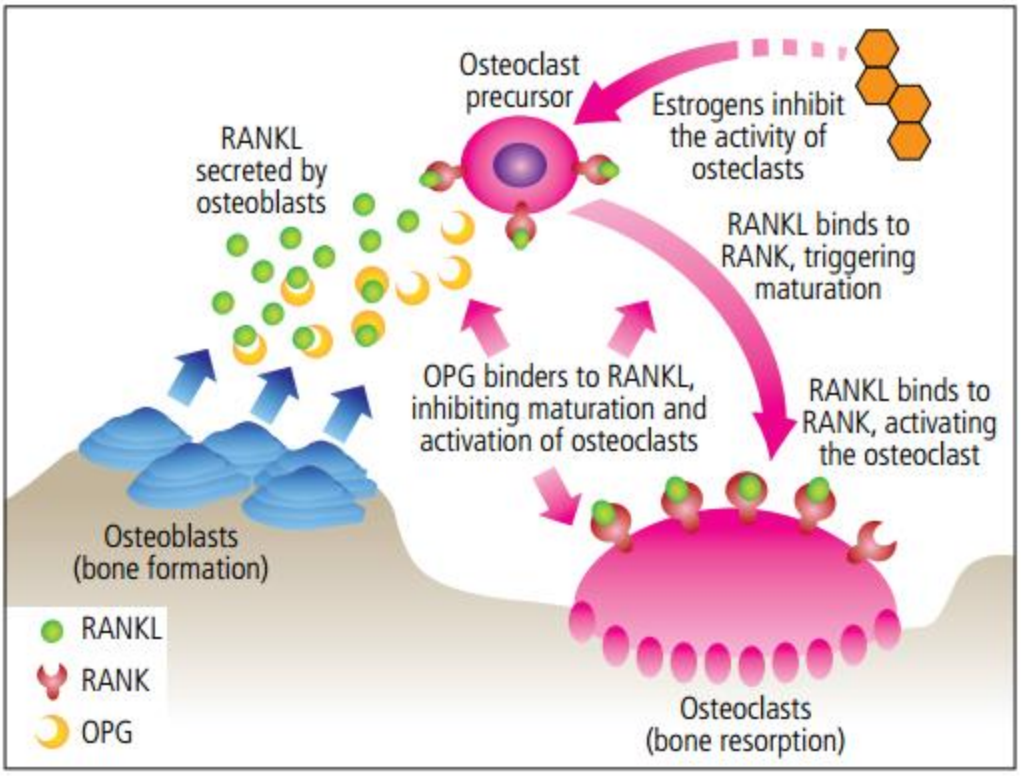


Figure 1.3 Bone remodelling cycle and the interplay between receptor activator of nuclear factor- B ligand (RANKL) and osteoprotegerin (OPG).

Osteoblasts express RANKL, which binds to its receptor (RANK) on the surface of osteoclasts precursors. These precursors then fuse to form the multinucleated osteoclasts. This binding also triggers differentiation, activation, and survival of osteoclasts. The binding of OPG to RANKL, blocks the differentiation and activation of new osteoclasts. (30) adapted from (38).

During this process osteoclasts, which are multinucleated cells formed through fusion of mononuclear precursors, dissolve bone mineral and enzymatically degrade the extracellular matrix to form bone resorbing pits (55). These pits are then lined with osteoblasts that produce collagen and other proteins to create a scaffold called the osteoid. This flexible surface is then mineralised, through deposition of hydroxyapatite, which results in rigid bone (55). Some osteoblasts become embedded in the bone matrix (55). The functions of osteoblasts and osteoclasts are regulated by many hormones, such as parathyroid hormone, androgens, vitamin D, and oestrogen (47). The regulation of bone remodelling by androgens and oestrogen is summarised in Figure 1.4.

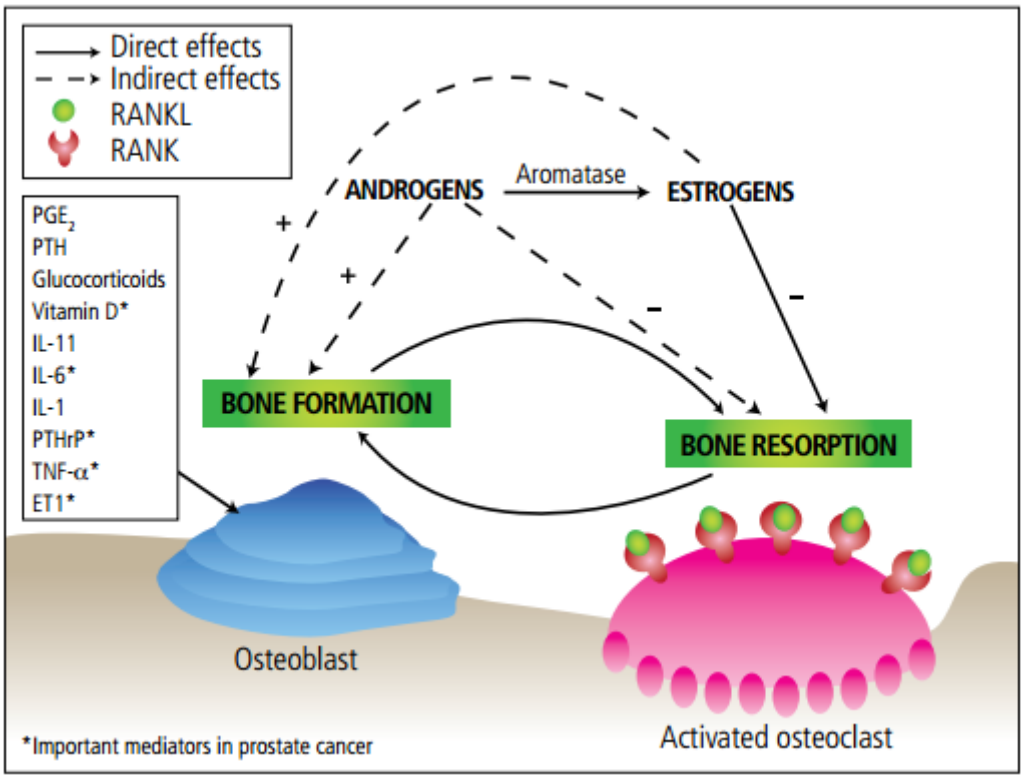


Figure 1.4 Hormonal regulation of bone remodelling.

Androgens promote bone formation while estrogen inhibits bone formation. During androgen or estrogen deficiency (e.g., during treatment with ADT or menopause) bone resorption predominates over bone formation, resulting in net bone loss. (30) adapted from (28).

1.3.2 **Health behaviours and risk factors for osteoporosis**

According to National Library of Medicine controlled vocabulary for PubMed citations indexing (MeSH terms), health behaviours are:

> *"behaviours expressed by individuals to protect, maintain, or promote their health status. For example, proper diet, and appropriate exercise are activities perceived to influence health status. Lifestyle is closely associated with health behaviour and factors influencing lifestyle are socioeconomic, educational, and cultural"* (57).

There are many lifestyle factors and health behaviours associated with osteoporosis and are presented in Table 1.3. The role of some of these health behaviours are discussed here.

Table 1.3 Risk factors for osteoporosis.

Modifiable risk factors	Non-modifiable risk factors
Poor calcium intake	Age
Vitamin D deficiency	Being female
Lack of weight-bearing exercise	Menopause
Low body weight	Hypogonadism[1]
Current cigarette smoking	Genetic predisposition
Excessive alcohol intake (≥ 3 standard drinks/day)	Diseases such as hyperparathyroidism, inflammatory bowel disease
Long term use of corticosteroids	History of diabetes

Sourced from (58)
[1]Androgen deficiency or suppression to castrate levels are referred to as hypogonadism.

Calcium is an essential bone nutrient as it is the major constituent of bone mineral (56). Vitamin D is needed for the absorption of calcium in the small intestines, for calcium homeostasis, and for bone remodelling (59). A constant supply of this mineral and vitamin are therefore needed for bone growth and remodelling, among other functions in the body. In childhood and early adulthood calcium in needed to optimise peak bone mass (60, 61) and in the remaining years this mineral is needed for bone maintenance rather than building new bone (62). Dairy products are an important source of calcium and contribute to bone health as evidenced by higher hip BMD observed in men with higher intakes of dairy products (63). Low levels of calcium intake are associated with increased risk of osteoporosis in men (64). A similar effect has been observed with calcium supplements or calcium with vitamin D supplements (800 IU) with a 12% reduction in fracture risk and reduced rate of bone loss (65). While this evidence supports the positive role of calcium on bone health, there are also studies reporting on the lack of effect of calcium on fracture risk (66). A meta-analysis by Bischoff-Ferrari, Dawson-Hugheset al. (66) reports that calcium (supplemental and dietary) was not associated with risk of fractures in prospective studies and randomised controlled trials. These authors attribute this apparent lack of effect to the flaws in calcium intake assessment tools, notably the food frequency questionnaire which poorly correlates with the gold standard in dietary data collection tools ($r = 0.4$) (67). The Women's Health Initiative study sheds more light on the discrepancy in the fracture risk reduction of calcium and vitamin D. This study reports on the reduced risks of hip fracture following long-term supplementation with calcium and vitamin D (HR 0.62), and a further risk reduction (HR 0.24) among women who were compliant in taking the supplements (68). The effect of greater fracture risk reduction in studies with higher compliance was also seen in the meta-analysis by Tang, Eslicket al. (65).

Exercise and physical activity are important lifestyle factors in bone health, with regular exercise recognised to maximise peak bone mass in childhood and reduce bone loss in adulthood (69). While more research is needed on the type of exercise and the long-term effects on bone health and fractures, the current evidence suggests that multi-modal exercise programs reduce the risks of osteoporosis and fractures (69, 70). It is also noted that the relationship between dietary calcium intake or physical activity and bone health is not linear and should not be considered in isolation from other environmental factors (64).

Current and/or past smoking increases the risks of low bone mass and is predictive of bone loss at the hips (71, 72). BMI and body weight are positively associated with hip BMD (72), while weight loss of >1% of body weight per year increases the risks of lower BMD (73). A study by Hannan, Felson et al. (74) found that weight gain slowed down bone loss, therefore indicating the loading effect that may be responsible for the positive association between body weight and BMD.

1.4 Significance of this thesis

There is ample evidence supporting poor bone health in men with prostate cancer, especially men on ADT, but less is known about the osteoporosis-related health behaviours that these men partake in. Before undertaking lifestyle interventions it is important to gather information about current health behaviours and practices, and psycho-behavioural and psycho–social factors driving such behaviours. This information can be used to underpin and tailor intervention programs targeted at managing poor bone health in specific groups. As such, the findings from this research program describe the determinants of health behaviours and current health behaviours (e.g. dietary), which are crucial to bone health, in men with prostate cancer and survivors.

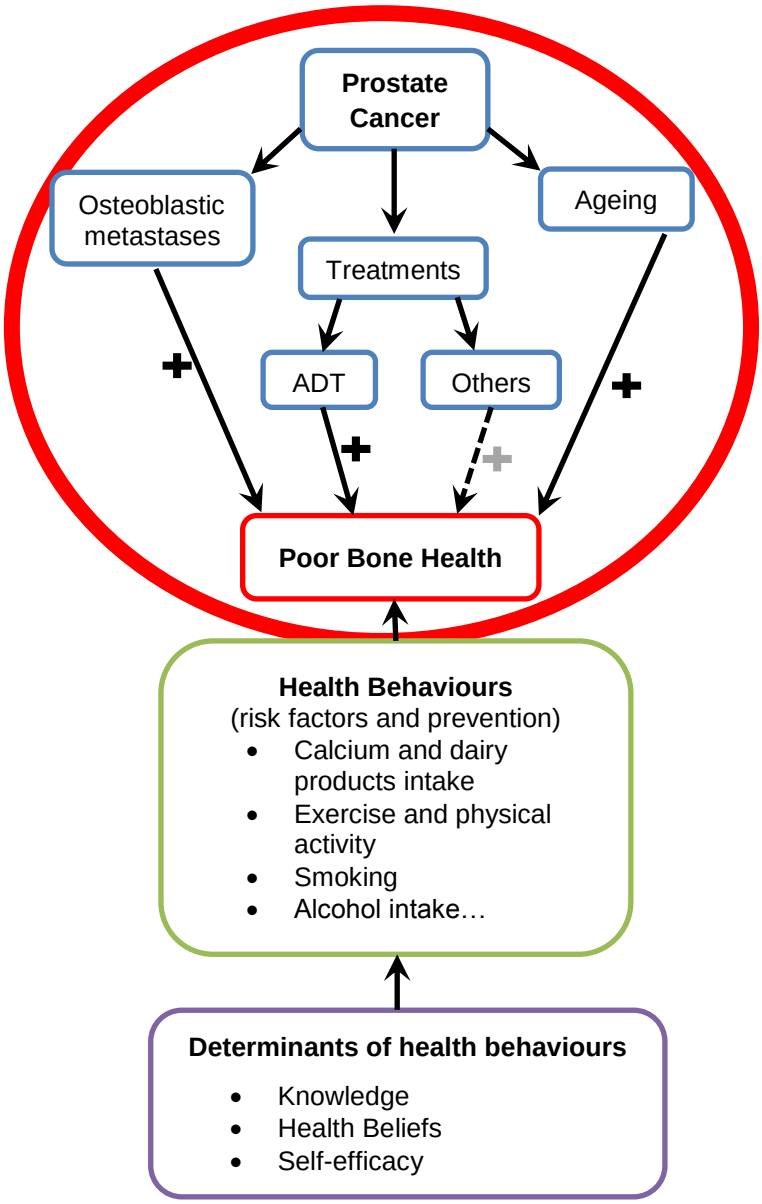
1.5 Purpose of this thesis

This research program consists of two meta-analyses, a review of the prostate cancer clinical guidelines (with a focus on bone health management recommendations), one study reporting on the secondary analysis of a large longitudinal dataset (DOES), and a cross-sectional study. The purpose of these studies is:

1. To explore the literature on the prevalence of osteoporosis and/or low bone mass (osteopenia) in men with prostate cancer, whether treated with ADT or not on ADT.

2. To explore bone health management recommendations for men with prostate cancer. The research questions addressed are:
    a. What are the bone-health management recommendations made in evidence-based guidelines for the management of prostate cancer?
    b. Do the recommendations include lifestyle management strategies, such as increasing dietary calcium and exercise/physical activity?
    c. If such recommendations are made, how detailed and comprehensive are they?
3. To determine the incidence of osteoporosis, osteopenia, and post-diagnostic fractures in men with BPH, men with prostate cancer not on ADT, and men with prostate cancer on ADT. The research questions addressed are:
    a. What is the post-diagnostic incidence of osteoporosis and/or low bone mass in men with BPH, men with prostate cancer on ADT, and hormone-naïve men with prostate cancer?
    b. What is the rate of post-diagnostic fractures in the population mentioned above?
4. To identify and describe the health behaviours and determinants of such behaviours in men with prostate cancer and survivors. The research questions addressed are:
    a. What is the extent of osteoporosis knowledge, osteoporosis-related health beliefs, and self-efficacy in men with prostate cancer and survivors?
    b. What are the health behaviours, notably dietary behaviours, that men with prostate cancer and survivors participate in? And are they adequate for optimum bone health?
    c. What is the association between determinants of health behaviours (psycho-behavioural and psycho–social factors), and bone health; and dietary behaviours in men with prostate cancer and survivors?

1.6 Review of the literature on the prevalence of osteoporosis in men with prostate cancer



Osteoporosis in men with prostate cancer is recognised and well-documented especially among men with prostate cancer on ADT. Unfortunately less attention has been paid to those not undergoing this treatment. This section therefore presents a review of the literature that synthesises the evidence on the prevalence of osteoporosis in men with prostate cancer, regardless of treatment. This section comprises two meta-analyses previously published in *Endocrine (75, 76)*.

1.6.1 **Prevalence of osteoporosis in men with prostate cancer on ADT**

This meta-analysis compiles the evidence on the prevalence of osteoporosis in men with prostate cancer on ADT. The studies were also mined to identify factors that could explain the pattern of prevalence observed here. The PhD candidate presented the results of this meta-analysis at The Prostate cancer World Congress 2013 as a moderated poster.

Citation: Lassemillante A-CM, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors: a meta-analysis. Endocrine. 2014;45(3):370-81.

Date submitted: 2nd July 2013
Date accepted: 11th October 2013

Please note that the reference style for this manuscript is that appropriate for the journal.

Prevalence of osteoporosis in prostate cancer survivors - A meta-analysis.

Annie-Claude M. Lassemillante[1,2], Suhail A. R. Doi[3], John D. Hooper[2], John B. Prins[2,4,] Olivia R. L. Wright[1,2]

Affiliations:

[1] Centre for Dietetics Research (C-DIET-R), School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, QLD 4072, Australia.

[2] Mater Research Institute – University of Queensland, Kent Street, Woolloongabba, QLD 4102, Australia.

[3] Clinical Epidemiology Unit, School of Population Health, The University of Queensland, Herston. QLD 4006, Australia.

[4] The University of Queensland Diamantina Institute, The University of Queensland, Woolloongabba, QLD 4102, Australia.

Abstract

Purpose: Androgen deprivation therapy (ADT), which is used in the treatment of prostate cancer (prostate cancer), is associated with increased morbidity. Severe bone loss is a major consequence of androgen ablation and with an increasing number of patients undergoing this treatment, the incidence of osteoporosis and fractures can be expected to increase with a significant impact on healthcare. To evaluate the prevalence of osteoporosis we conducted a review of the literature on bone health in men with prostate cancer undergoing ADT. *Method:* A meta-analysis was conducted using the quality effects model and sources of heterogeneity were further explored by consideration of discordant effect sizes of included studies in the meta-analysis and examining reasons thereof. *Results:* Our analyses indicate that the prevalence of osteoporosis varies between 9 and 53% with this variation partially explained by treatment duration, disease stage, ethnicity and site of osteoporosis measurement. *Conclusion:* While it is well known that a rapid decline in bone health among men with prostate cancer on ADT occurs, this meta-analysis documents the high prevalence of osteoporosis in this population and reinforces the need of preventative approaches as part of usual care of prostate cancer patients.

Introduction

Androgen deprivation therapy (ADT) is used in the management of locally advanced and metastatic androgen-dependent prostate cancer [1,2]. As a result there are an increasing number of males living with hypogonadal levels of testosterone making ADT a contemporary cause of severe male hypogonadism [3]. Unfortunately ADT has been associated with adverse effects such as gynecomastia, sexual dysfunction, increased fat mass, metabolic syndrome and bone loss [4,5] all of which have a significant impact on the quality of life of prostate cancer patients [4].

Of particular concern is the fact that ADT has been shown to significantly decrease bone mineral density (BMD) by 1.5-4.0% annually [6], which exceeds that of healthy ageing males [6] and that of postmenopausal women, who experience an annual bone loss of 2.5% [6,7]. The estimated lifetime risk of experiencing an osteoporotic fracture in men aged over 50 years is 13.0% [8] while prostate cancer patients exhibit a 21.0-37.0% increase in this risk [6]. Although it is well-accepted that hypogonadism is responsible for severe bone loss in prostate cancer patients on ADT [9], there has been less emphasis on the burden of this problem or associated factors. Therefore this meta-analysis aims to compile evidence from the literature on the impact of ADT on the bone health of prostate cancer patients while identifying other factors that may help explain patterns in osteoporosis prevalence.

Methods

A systematic review was carried out using the guidelines published by Littell et al. [10] and the PRISMA statement [11] was used to guide reporting. A protocol has not been previously registered.

Data sources

We conducted a systematic literature search of EMBASE, PUBMED and SCOPUS for studies published until December 2012. The databases were searched using the respective controlled vocabulary of terms for “prostate cancer” and “osteoporosis” or “bone loss” (see Appendix III for more details) except for Scopus. Studies were limited to those carried out in humans and published in English.

Study selection and eligibility criteria

Prospective longitudinal and cross-sectional studies were considered for review and exclusions were made if studies were case reports, conference abstracts, letters to editors, did not report on the prevalence of osteoporosis, did not differentiate between osteoporosis and osteopenia and did not categorize men by ADT status.

Data extraction and eligibility criteria

The data extracted included study year and study type, number of participants, type and duration of prostate cancer treatment, cancer stage and grade, metastatic status, prevalence of osteoporosis, osteopenia and normal bone mass, method used to determine bone health, region of interest (ROI) scanned, country where study was conducted and ethnicity. Each study was assessed using a quality assessment checklist developed from the “Risk of bias tool” from Hoy et al. [12] with a maximum score of 10. This tool allowed for checking of ten items that protect against bias in prevalence studies with four items relating to external validity and six to internal validity. Shortfalls in any of the two validity domains are known to lead to bias in prevalence studies [12]. Therefore, studies with up to four protective measures (score ≤ 4) had a high risk of bias (ROB), those with 5 to 7 measures had a moderate ROB and those with eight or more measures (score ≥ 8) had a low ROB. Methodological quality was also evaluated using this checklist. Additionally, the meta-analysis model redistributed the inverse variance weights of individual studies based on the quality information, with the higher quality studies having less re-distribution of weight (final weights reported in Figure 1.6, Figure 1.7, and Figure 1.8). Thus quality stratification or sensitivity analysis by quality was not required. Finally, the funnel plot, a common method of checking for publication bias, could not be used due a high degree of heterogeneity between the studies; hence asymmetry on the latter plot would be attributed to heterogeneity rather than publication bias [13]. Furthermore, it is expected that asymmetry resulting from distinct subgroups will no longer be seen when a plot is done for each subgroup [14].

Statistical methods

The primary outcome was prevalence of normal bone mass, osteopenia and osteoporosis as defined by World Health Organization osteoporosis diagnostic criteria [15]. This prevalence was stratified into more homogenous subgroups by classifying the studies into low (<15.0%), moderate (15.0-45.0%) and high (>45.0%) osteoporosis based on the data

reported within the studies. All analyses were performed on the double arcsine square root transformed proportion and results were back transformed to the natural scale.

Heterogeneity was determined to be present when the value of τ^2 was greater than zero and/or the Q-statistic was significant at a P < 0.1 [16]. Although the standard approach for handling heterogeneity between studies is to use the random effects model [17], the present study used bias adjustment via the quality effects model [18,19] as the random effects model estimates have been shown to lack real interpretability [20]. The results from the random effects model were however noted for comparative purposes in online resource material 2. Robustness of our meta-analysis was explored using sensitivity analyses created through altering selection criteria of the studies. Sources of heterogeneity were further explored by consideration of discordant effect sizes of included studies in the meta-analysis and examining reasons thereof. All analyses were done using MetaXL version 1.32 (www.epigear.com).

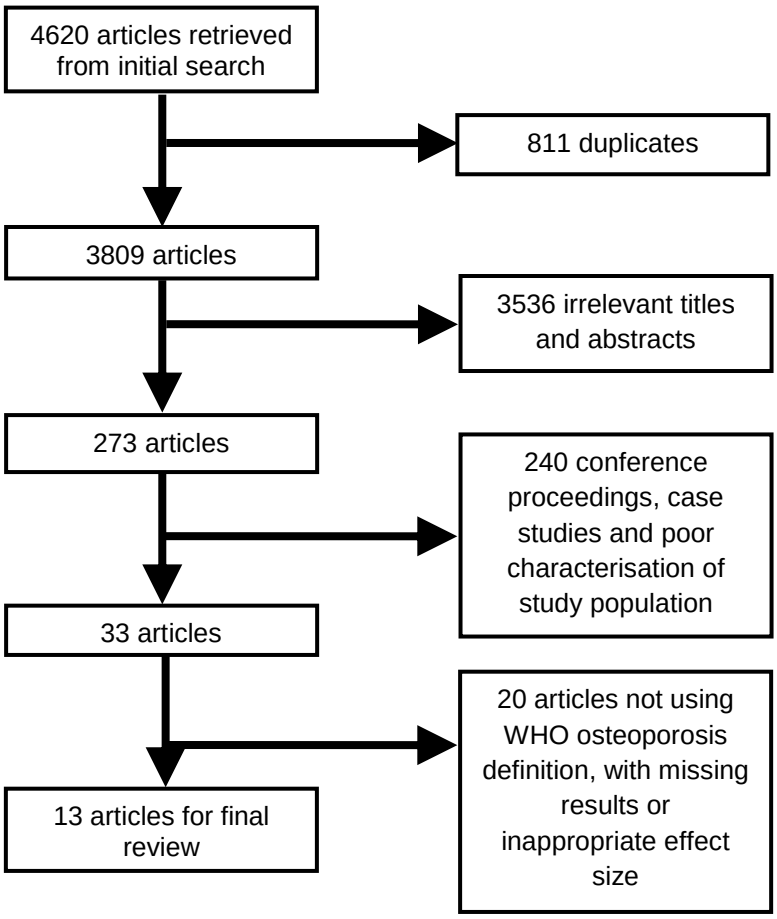


Figure 1.5 Flow diagram of study selection used in this meta-analysis.

Results

Characteristics of the studies

The search from EMBASE, PUBMED and SCOPUS identified 3809 unique abstracts. After elimination of irrelevant articles, case studies and conference abstracts, 33 articles were reviewed. Of these, only 13 reported on osteoporosis and osteopenia prevalence and have been included in this meta-analysis (Table 1.4).

The studies reviewed here were published between 1999 and 2012, were all cross-sectional except for two studies [21,22]. Studies were from Japan [23,24], China [25], Australia [26], USA [27,28,21,29,22] and Europe [30-33]. The total number of men with prostate cancer on ADT was 1394 with a median age of 72.9 years (range 64.5-80.0 years) and median ADT duration of 28.5 months (range 16.0-53.2 months). All the studies used dual-energy X-ray absorptiometry (DXA) to determine BMD and the World Health Organization osteoporosis diagnostic criteria, with some studies accounting for race [23-25] by using an ethnic appropriate normative database rather than using the National Health and Nutrition Examination Survey (NHANES) reference database (a Caucasian population [34]). The ROIs used in the studies were hip (femoral neck; FN), lumbar spine and distal third of the radius. Most studies included here reported osteoporosis as present if observed at any of the reviewed sites [21-27,29-31,33]; therefore the exact ROI affected could not be differentiated. Only two studies reported osteoporosis at FN only [28] or distal third of the radius only [32]. Primary gonadal ablation therapy (bilateral orchiectomy [25] or treatment with gonadotropin-releasing hormone (GnRH) agonists [21,27,29,32]) or combined androgen blockade (CAB; the latter in conjunction with androgen receptor antagonists [22-24,26,28,30,31,33]) were the two main ADT modalities. Disease stage or grade was not well described across studies but all reported on the presence or inclusion of soft tissue or bone metastases in their analyses.

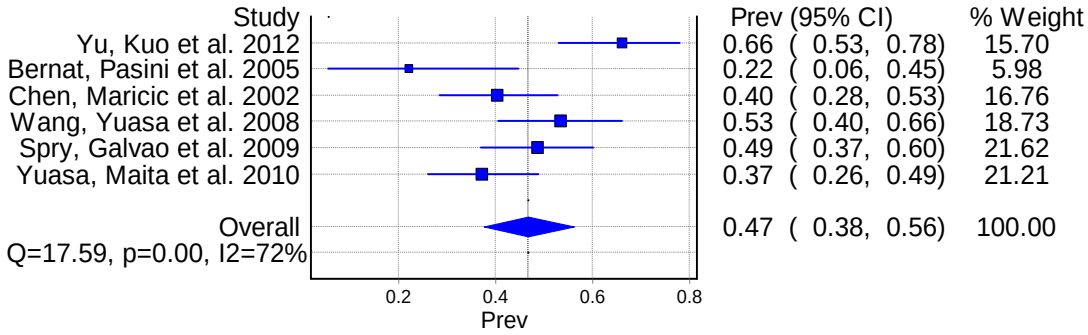
Table 1.4 Characteristics of studies reviewed.

Study name	Study subjects (N)	Study design	Population description Age (mean±SD or median (range)), Ethnicity, Country, disease stage/grade, recruitment year if available	Exclusion criteria	Types of treatments received	Quality score
Sieber, Rommel et al. 2012 [21]	343	Retrospective	80 years (54-95 years), Caucasian, USA, No details on disease stage/ grade	Prior hip replacement	GnRH agonists with or without non-steroidal anti-androgens, and orchiectomy	6
Yu, Kuo et al. 2012 [22]	56	Prospective trial	64.5years (49.8- 80.9 years), mostly, Caucasian, USA, Stage A2-D1 (American Urological Association system), 1996-2006	Presence of bone metastases, prior bisphosphonates treatment, no DXA scan at baseline	GnRH agonists and non-steroidal anti-androgens (initiated 2 weeks prior to GnRH agonists) for 9 months This cycle re-initiated upon disease progression.	6
Wang, Yuasa et al. 2008 [23]	58	Cross-sectional	68.5±7.7 years and 72.8±7.1 years (for patients with and without bone metastases respectively), Asian, Japan, Gleason 8.1±1.3 and 7.4±1.5 (for patients with and without bone metastases respectively), 2006-2007	Presence of bone metastases at hip or lumbar spine	GnRH agonists and/or orchiectomy and non-steroidal anti-androgens or both modalities alone	7
Yuasa, Maita et al. 2010 [24]	70	Cross-sectional	71.1±7.7 years and 74.1±6.2 years (for patients with and without bone metastases respectively), Asian, Japan, Gleason 8.0±1.3 and 7.7±1.4 (for patients with and without bone metastases respectively), 2006-2009	Presence of bone metastases at hip or lumbar spine	GnRH agonists and/or orchiectomy and non-steroidal anti-androgens or both modalities alone	7
Deng, Yang et al. 2004 [25]	28	Cross-sectional	71 years (65-83 years), Asian, Taipei, Stage C or D (Whitmore-Jewett Staging system), 1999-2002	Secondary cause of osteoporosis, drugs affecting bone metabolism	GnRH agonists or orchiectomy	6
Spry, Galvao et al. 2009 [26]	72	Prospective Longitudinal	73.5±8.8 years (44.4-88.4 years), Caucasian, Australia, locally and distally advanced disease (excluding bone metastases), 1999-2002	Presence of bone metastases	GnRH agonists depot at baseline, 3 and 6 months and non-steroidal anti-androgens for 9 months.	7

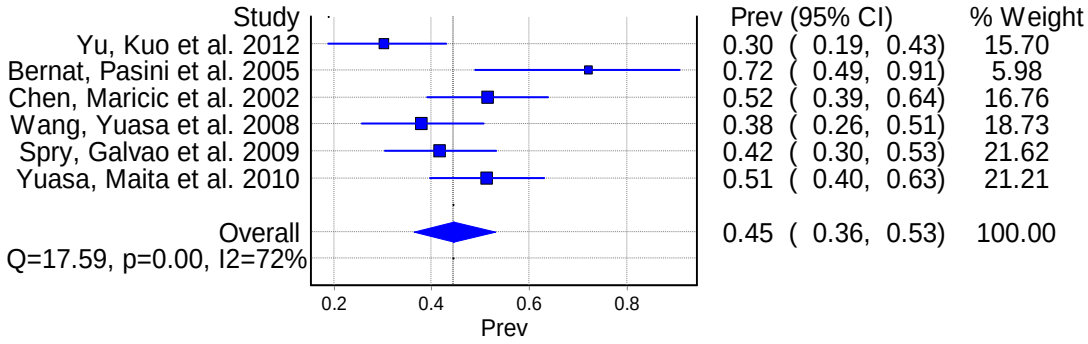
					This cycle re-initiated upon disease progression.	
Bruder, Ma et al. 2006 [27]	89	Retrospective	77±7 years, mostly Caucasian and Hispanic, USA, No details on disease stage/grade	Prior bone disease	GnRH agonists or orchiectomy	8
Chen, Maricic et al. 2002 [28]	62	Cross-sectional	74.3years, mostly Caucasian, USA, Stage C or D (Whitmore-Jewett Staging system)	Intermittent-ADT, active or hormonally refractive prostate cancer, presence of bone metastases at hip or lumbar spine, prior surgery at hip or lumbar spine	GnRH agonists and non-steroidal anti-androgens	6
Wei, Gross et al. 1999 [29]	24	Cross-sectional	73 years (71-76 years), Caucasian and African American, USA, No details on disease stage/grade	Documented secondary cause of osteoporosis, drugs affecting bone metabolism	GnRH agonists or orchiectomy	7
Bernat, Pasini et al. 2005 [30]	18	Cross-sectional	53-78 years, Caucasian, Croatia, No details on disease stage/ grade, 1999-2002	Prior treatment with ADT or bisphosphonates, or treatment with drugs affecting bone metabolism	GnRH agonists and non-steroidal anti-androgens	4
Morote, Morin et al. 2007 [31]	266	Cross-sectional	68.9±7.3 years, Mediterranean, Spain, mean Gleason 6.8±1.6	Prior radiotherapy, presence of bone metastases, treatment with drugs affecting bone metabolism	GnRH agonists and non-steroidal anti-androgens	7
Peters, Fairney et al. 2001 [32]	42	Cross-sectional	76.7±0.98 years, No details on ethnicity, UK,median Gleason 5	Presence of bone metabolic diseases	GnRH agonists	4
Planas, Morote et al. 2007 [33]	266	Cross-sectional	71.0 years (53.0-89.0 years), Mediterranean, Spain, mean Gleason 7	Presence of bone metastases, secondary causes of osteoporosis	GnRH agonists	7

prostate cancer, prostate cancer; ADT, androgen deprivation therapy; GnRH, gonadotropin releasing hormone.

a. Normal



b. Osteopenia



c. Osteoporosis

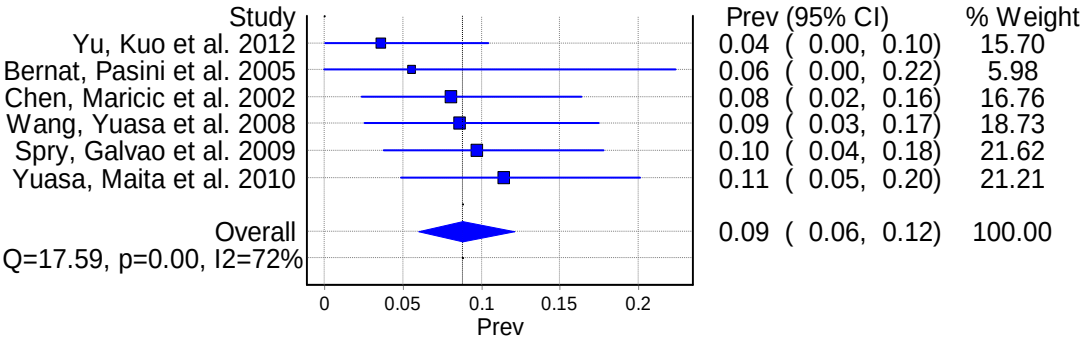
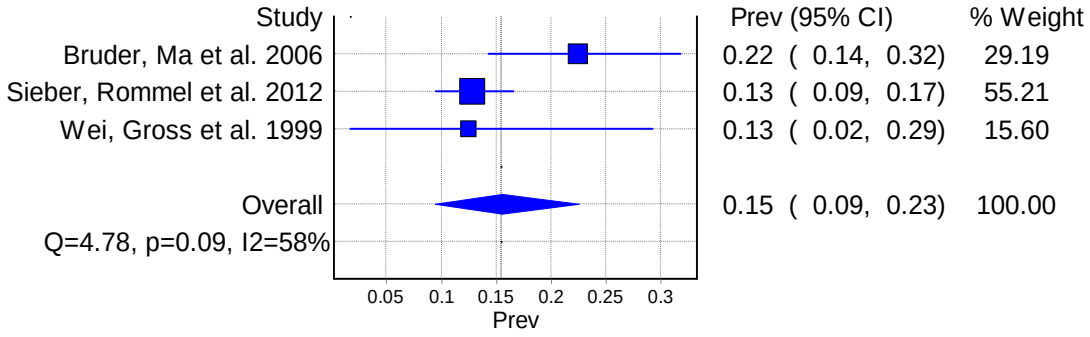
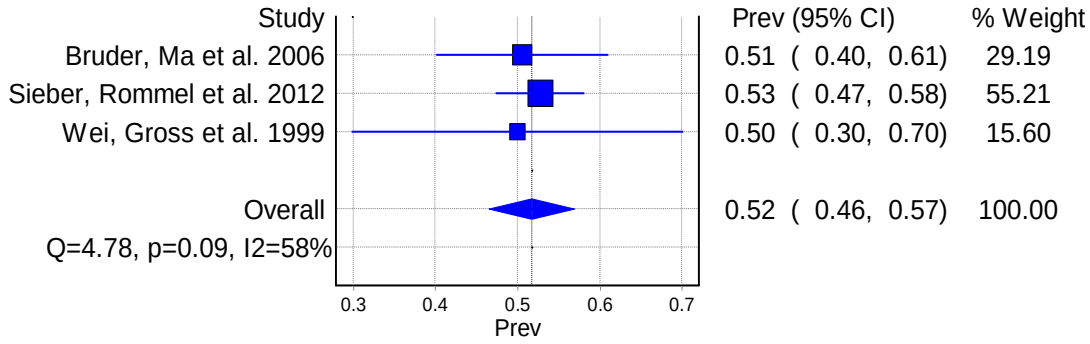


Figure 1.6 Stratum of low prevalence of osteoporosis - range 6.0-12.0%; pooled 9.0%.

a. Normal



b. Osteopenia



c. Osteoporosis

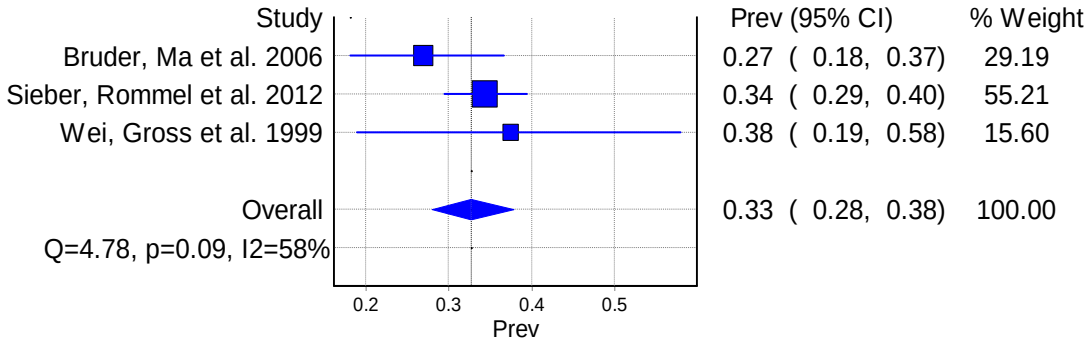
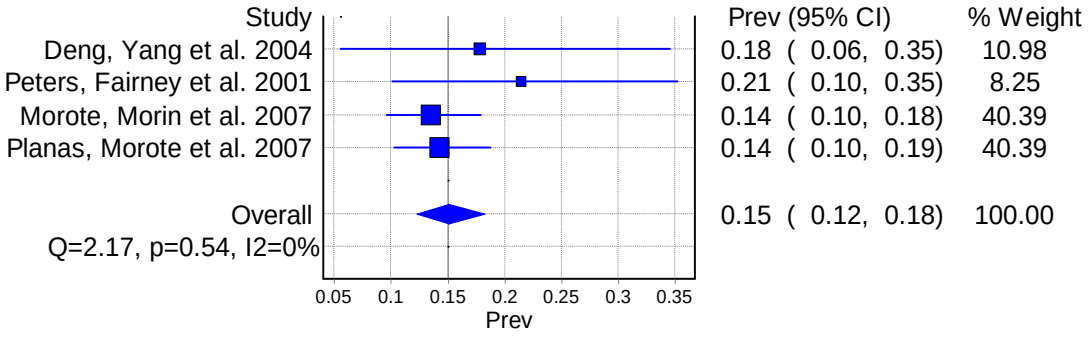
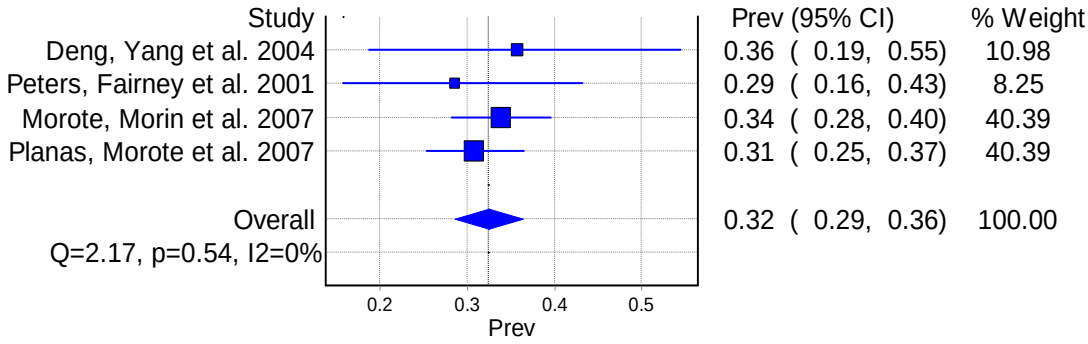


Figure 1.7 Stratum of moderate prevalence of osteoporosis - range 28.0-38.0%; pooled 33.0%.

a. Normal



b. Osteopenia



c. Osteoporosis

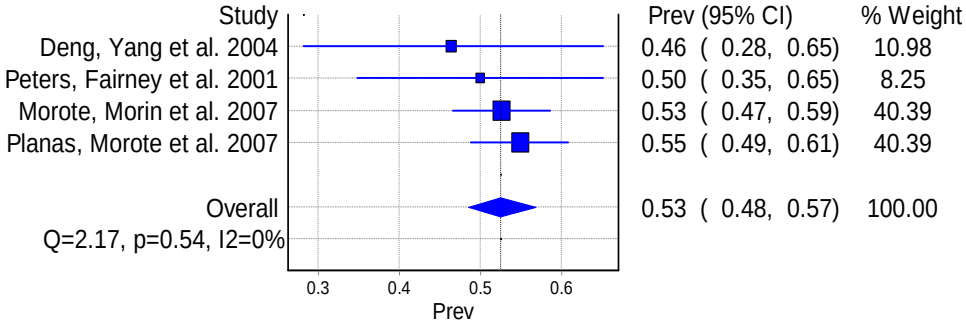


Figure 1.8 Stratum of high prevalence of osteoporosis - range 48.0-57.0%; pooled 53.0%.

Quantitative synthesis by osteoporosis stratum

Low prevalence of osteoporosis

Six studies reported a prevalence of osteoporosis under 15.0% [23,24,26,28,22,30]. The pooled prevalence of osteoporosis was 9.0% (95% CI: 6.0%-12.0%) and normal bone mass was the predominant group at 47.0% (95% CI: 38.0%-56.0%). The exact ADT duration in this subgroup could not be quantified due to two studies [26,22] reporting on intermittent ADT. This latter treatment involved a number of cycles of androgen ablation interspersed with cessation of therapy until PSA rose above 20ng/mL. Hence, the number of months on treatment was different across participants in these studies, and the authors

also noted that BMD recovered during the treatment cessation periods. Men in this subgroup were younger (median 71.0 years, IQR 5.7) than the moderate osteoporosis subgroup (median 75.7 years, IQR 3.7). Interestingly, CAB was quite frequent among studies in this subgroup [24,26,22,30]. The median ROB score for this subgroup was 6.5 (range 4-7), and was found to be similar to the scores of the high osteoporosis subgroup.

Moderate prevalence of osteoporosis

Three studies reported a prevalence of osteoporosis between 15.0-45.0% [27,21,29]. Pooled prevalence of normal bone mass was now much lower than the previous subgroup at 15.0% (95% CI: 9.0%-23.0%) while osteopenia and osteoporosis were much higher at 52.0% (95% CI: 46.0%-57.0%) and 33% (95% CI: 28%-38%) respectively. The ROB scores for these studies ranged between 6 and 8 (median 7). The duration of ADT varied between 16.0 months and 43.0 months (median 32.4 months) and studies reported on use primary gonadal androgen ablation only. All these studies also used radial BMD in addition to hip or lumbar spine, in the diagnosis of osteoporosis.

High prevalence of osteoporosis

Four studies reported a prevalence of osteoporosis over 45.0 % [25,31-33]. Here the prevalence of normal bone mass remained similar to the previous group (15.0%; 95% CI: 12.0%-18.0%) while the prevalence of osteoporosis was higher (53.0%, 95% CI: 48.0%-57.0%) and of osteopenia was lower. An even number of studies reported on the use of primary gonadal androgen deprivation and CAB. All except Deng et al. [25], used the NHANES database when diagnosing osteoporosis. All the studies in this subgroup only included men with metastatic disease demonstrating advanced prostate cancer.

Sensitivity analyses and publication bias

There was a trend towards worse bone health with longer ADT duration, as osteoporosis prevalence increased. An inverse trend could be seen in the prevalence of normal bone mass with ADT duration and studies investigating ADT for <24months (or intermittent-ADT) reported the highest prevalence of normal bone mass (see Table 1.5).

Studies reporting on non-Asian males reported a higher prevalence of osteoporosis than those reporting on their Asian counterparts (34.7%; 95% CI: 23.3%-44.9% versus 15.8%; 95% CI: 4.3%-30.9%). Studies measuring osteoporosis at a site that included the radius also reported a higher prevalence of osteoporosis and osteopenia (34.3% and 49.6%

versus 31.4% and 40.0% respectively) than studies measuring osteoporosis at sites excluding the radius. Therefore the addition of this ROI led to a higher detection of poorer bone health.

The prevalence of osteoporosis and osteopenia were similar in studies investigating the impact of primary gonadal androgen ablation or CAB. Also, studies of younger prostate cancer participants reported a similar prevalence of osteoporosis as subjects aged 70 years and over (see Table 1.5).

In terms of risk of bias, two studies were deemed high risk [30, 32], ten were deemed moderate risk [21-26, 28, 29, 31, 33] and one low risk [27] on the “Risk of bias tool” as defined in the methods section [12]. The most common deficiency among the moderate group was selection bias as most authors recruited participants from local health care centres, which may not be representative of the prostate cancer population at large. The two studies [30,32] classified as high ROB, mainly had poor external validity and thus exhibited deficiencies on the following items: the target population, randomisation, reporting of the sampling frame and non-response bias. Consequently under the meta-analysis model used, these studies contributed much less to their respective subgroup’s pooled estimate. Numbers of non-deficient items (quality score) for each study are listed in Table 1.4.

Discussion

The results presented here quantify the prevalence of osteoporosis and osteopenia in prostate cancer patients on ADT, with the majority of these patients experiencing poor bone health (up to 85.0%). The variation in the prevalence of osteoporosis (9.0%-53.0%) observed in this paper seems to be influenced by ADT duration, disease stage, ethnicity and skeletal site used to diagnose osteoporosis. The effects of ADT on bone mass are well recognized in the literature and a prior meta-analysis by Neto et al. [9] reported an increase in the risk of developing osteoporosis in prostate cancer patients on ADT. Our meta-analysis is the first to compile the prevalence of osteoporosis from the literature and to document the extensive disparity in prevalence of osteoporosis in this population, therefore revealing an important clinical heterogeneity worthy of further investigation.

Table 1.5 Sensitivity analyses.

Studies selected if:	Osteoporosis prevalence (95% CI)	Osteopenia prevalence (95% CI)	Normal bone mass prevalence (95% CI)
Age			
≥70 years [19, 21-27,30]	0.270 (0.176-0.361)	0.485 (0.420-0.526)	0.245 (0.158-0.331)
<70 years [20,28,29,31]	0.436 (0.233-0.612)	0.361 (0.261-0.434)	0.204 (0.074-0.351)
Publication year			
<2007 [23,25-28,30]	0.270 (0.156-0.391)	0.487 (0.387-0.573)	0.244 (0.172-0.316)
≥2007 [19-22,24,29,31]	0.329 (0.193-0.450)	0.416 (0.317-0.482)	0.255 (0.141-0.362)
Ethnicity			
Asian population [21-23]	0.158 (0.043-0.309)	0.444 (0.338-0.530)	0.398 (0.241-0.546)
`Non-Asian population [19,20,24-31]	0.347 (0.233-0.449)	0.432 (0.345-0.495)	0.221 (0.137-0.302)
Median ADT duration			
<24 months / intermittent [19,20,24,28]	0.198 (0.067-0.346)	0.506 (0.367-0.594)	0.297 (0.114-0.485)
24-30 months [21,23,26,30]	0.202 (0.067-0.363)	0.416 (0.307-0.500)	0.381 (0.236-0.510)
>30 months [22,25,27,29,31]	0.427 (0.279-0.568)	0.395 (0.301-0.480)	0.179 (0.110-0.253)
ROI			
Hip / lumbar spine [20-24,26,28,29,31]	0.314 (0.187-0.426)	0.400 (0.320-0.445)	0.287 (0.179-0.381)
Third distal radius (alone or with hip/lumbar spine) [19,25,27,30]	0.343 (0.270-0.420)	0.496 (0.420-0.588)	0.161 (0.108-0.222)
ADT			
Primary gonadal ablation therapy [19,23,25,27,30]	0.355 (0.287-0.426)	0.482 (0.397-0.567)	0.164 (0.119-0.214)
Combination androgen blockade [20-22,24,26,28,29,31]	0.302 (0.170-0.422)	0.402 (0.317-0.452)	0.295 (0.179-0.396)

Disease stage: Metastasis

This meta-analysis demonstrated that the highest prevalence of osteoporosis occurred in men with metastatic disease probably as a result of disease pathophysiology. This can be due to an increase in bone resorption, as evidenced by elevated N-telopeptide levels seen upon disease progression [35]. There are suggestions that bone resorption is necessary to release growth factors that allow prostate cancer bone metastases to appear in the skeleton [36]. This is a complex process, whereby prostate cancer cells secrete pro-osteolytic factors that increase bone resorption and the release of various growth factors from the bone [37,38]. These factors are believed to modify the bone microenvironment and the prostate cancer cells phenotype [37] leading to the development of osteoblastic

metastases. Therefore it is hypothesized that an increase in skeletal metastatic foci, is preceded by an increase in bone resorption to allow prostate cancer cells to niche to active resorption sites. Unfortunately, this model is based on *in vitro* and animal models and such research involving prostate cancer patients remains challenging due to the confounding effects of treatments, such as ADT, on bone metabolism. Besides, the high osteoporosis prevalence can also be associated with longer duration of ADT in such cases as a result of a longer life with prostate cancer. While it is well accepted that ADT will lead to severe bone loss in men with localized prostate cancer [6], the longitudinal effects of ADT on bone resorption in men with metastatic prostate cancer are confounded by the disease stage [35,39,40] therefore limiting the conclusions that can be drawn.

ADT duration

Testosterone is known to affect bone cells through the androgen receptor (AR), for instance androgens will increase osteoblast proliferation while inhibiting osteoblast apoptosis [41]. Therefore upon androgen deprivation, there is an imbalance between bone formation and degradation resulting in net bone loss as indicated by elevated levels of bone resorption biomarkers [42]. Additionally, decreases in testosterone levels also lead to a decrease in aromatization to estrogen and while both hormones seem to be important for bone formation, it seems that estrogen is the major sex steroid regulating bone resorption even in men [43]. This change in bone metabolism with ADT leads to the decrease of bone mass over time [42] and was demonstrated in the sensitivity analyses that revealed an increase in the prevalence of osteoporosis with ADT duration. Although there is a link between ADT, body composition changes [44] and bone resorption biomarkers, this could not be quantified here due to lack of reporting of these parameters in the studies reviewed.

Type of ADT

Our results indicated that the type of ADT used impacted less on bone loss, whereby patients on primary gonadal ablation or CAB seem to experience a similar prevalence of osteoporosis and osteopenia. This is consistent with a previously published review on the long-term side effects of ADT by Alibhai et al. [45], where the authors could not differentiate between the impact of the two ADT modalities on bone loss. Androgen ablation is associated with an increase in bone resorption, as evidenced by increased levels of N-telopeptide [46], therefore is also associated with a higher mean percentage yearly decrease in BMD [6], as a result of an increase in cortical porosity and decrease trabecular number [47]. Increases in clinical fractures after treatment with GnRH agonists

or CAB have been documented [48]. The latter study reported a higher hazard of fractures among men treated with CAB than GnRH agonists [48] while Smith et al. [49] reported elevation in fracture risk when prostate cancer patients are treated with GnRH agonists for at least one year. It is important to note that about 15.0% of fractures seen in men with prostate cancer are pathologic in nature suggesting that any differences in osteoporosis prevalence may be due to variations in disease characteristics (and associated co-morbidities) than treatment per se [48].

Osteoporosis site and age

There may be erroneously elevated BMD at the lumbar spine as a result of osteoarthritis rendering the spine unsuitable, or after hip replacement rendering the FN unsuitable. Therefore, BMD measurement practices and age of subjects will also impact on the prevalence of osteoporosis as outlined by some studies reviewed here [21,29]. The inclusion of distal third radius T-scores, which is only recommended when other ROIs are not suitable, has led to a slight increase in the prevalence of osteoporosis and osteopenia in prostate cancer patients on ADT [27]. This increase in prevalence when adding distal third radius to other ROIs can be explained by the fact that the trabecular content of the distal third radius is known to increase with age [50]. Besides, bone loss is more severe at trabecular sites, with a higher remodelling surface, than cortical sites [51]. Evidence from high-resolution peripheral quantitative computed tomography has shown that increased porosity at cortical bone, trabecularization of cortical bone and loss of trabecular bone all occur in androgen deprived prostate cancer patients [47]. Age had a minimal impact on the prevalence of osteoporosis probably because of the small difference in median ages between the two groups while ADT may have masked the typical longitudinal changes in BMD in elderly males [6].

Ethnicity

The use of race appropriate reference groups in determining T-scores also affected the prevalence of osteoporosis in the current population and is likely to be similar in other populations [52]. The International Society for Clinical Densitometry (ISCD) recommends to use the NHANES III database when diagnosing osteoporosis rather than accounting for race [53]. Sensitivity analysis by ethnicity demonstrates that non-Asian prostate cancer patients are more prone to osteoporosis but an explanation cannot be offered as studies investigating both ethnicities used different normative database to diagnose osteoporosis. This finding outlines the importance of consistent bone health monitoring while following

current ISCD guidelines. It may also warrant early pharmacological management of osteoporosis [6] in certain ethnic groups.

Limitations and conclusions

The studies included in this meta-analysis did not report on any co-morbidity data, dietary, exercise or lifestyle factors that are known to affect bone mass. Although these would impact on bone health of prostate cancer patients, we cannot make any conclusions whether differences in these may help explain the variation that is seen in the current prevalence of osteoporosis. This evident gap in the literature warrants further research on these factors and their impact on osteoporosis in prostate cancer patients. Additional limitations include the possible exclusion of data from studies not published in English and studies which did not differentiate between osteopenia and osteoporosis. We suspect that such data would have a minimal effect on the pooled estimates while narrowing the confidence intervals. The funnel plot was excluded due to its inherent flaws with interpretability given the high degree of heterogeneity between the studies in this meta-analysis; therefore publication bias could not be determined. However, adjustment for other possible biases has been undertaken through the use of the quality effects model.

prostate cancer patients now live longer [54] and are increasingly treated with ADT. This meta-analysis suggests that over 50.0% of patients will suffer from osteoporosis if treated with ADT for approximately 3 years. Unfortunately, there is evidence suggesting that DXA scanning and interventions, such as promotion of healthy bone behaviours, are poorly implemented at initiation of ADT [55] despite the presence of other osteoporosis risk factors and co-morbidities [56]. Moreover, it was found that such patients lack basic osteoporosis knowledge and do not engage in healthy bone behaviours such as participating in physical exercise and consuming adequate calcium and vitamin D [57]. There is thus a real need to initiate the bone health conversation between the prostate cancer patient and treating health professional as this issue is currently overlooked [56,58]. Finally, current recommendations do not include the addition of an osteoclast inhibitor therapy (bisphosphonates, RANKL inhibitor) in men without bone metastases who are treated with long-term ADT unless the 10-year probability of hip fracture is ≥3.0% or the 10-year probability of a major osteoporosis-related fracture is ≥20.0% [59]. Recent reviews on the cotemporary management of osteoporosis have outlined the superiority of RANKL inhibitors over bisphosphonates in reversing the impact of ADT on BMD as well as the reductions in skeletal related events in prostate cancer patients [60,61]. The evidence

presented here therefore reinforces the need for preventative strategies such as calcium and vitamin D supplementation [6], and early osteoporosis pharmacological interventions, prior to ADT initiation to avoid the deleterious effects of osteoporosis related morbidity in prostate cancer patients.

References

1. Harris, W.P., Mostaghel, E.A., Nelson, P.S., Montgomery, B.: Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. Nat. Clin. Prac. Oncol. **6**(2), 76-85 (2009). doi:10.1038/ncpuro1296

2. Sharifi, N., Gulley, J.L., Dahut, W.L.: Androgen deprivation therapy for prostate cancer. JAMA **294**(2), 238-244 (2005). doi:10.1001/jama.294.2.238

3. Grossmann, M., Hamilton, E.J., Gilfillan, C., Bolton, D., Joon, D.L., Zajac, J.D.: Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy. Med. J. Aust. **194**(6), 301-306 (2011).

4. Herr, H.W., O'Sullivan, M.: Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. J. Urol. **163**(6), 1743-1746 (2000). doi:http://dx.doi.org/10.1016/S0022-5347(05)67533-7

5. Taylor, L.G., Canfield, S.E., Du, X.L.: Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. Cancer **115**(11), 2388-2399 (2009). doi:10.1002/cncr.24283

6. Higano, C.S.: Androgen-deprivation-therapy-induced fractures in men with nonmetastatic prostate cancer: what do we really know? Nat. Clin. Prac. Oncol. **5**(1), 24-34 (2008).

7. Seifert-Klauss, V., Fillenberg, S., Schneider, H., Luppa, P., Mueller, D., Kiechle, M.: Bone loss in premenopausal, perimenopausal and postmenopausal women: results of a prospective observational study over 9 years. Climacteric **15**(5), 433-440 (2012). doi:10.3109/13697137.2012.658110

8. Melton, L.J., Chrischilles, E.A., Cooper, C., Lane, A.W., Riggs, B.L.: How many women have osteoporosis? J. Bone Miner. Res. **20**(5), 886-892 (2005). doi:10.1359/jbmr.2005.20.5.886

9. Neto, A.S., Tobias-Machado, M., Esteves, M.A., Senra, M.D., Wroclawski, M.L., Fonseca, F.L., dos Reis, R.B., Pompeo, A.C., Del Giglio, A.: A systematic review and meta-analysis of bone metabolism in prostate adenocarcinoma. BMC Urol. **10**(1), 9 (2010). doi:10.1186/1471-2490-10-9

10. Littell, J.H., Corcoran, J., Pillai, V.K.: Systematic reviews and meta-analysis. Pocket guides to social work research methods. Oxford University Press, (2008)
11. Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G.: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. J. Clin. Epidemiol. **62**(10), 1006-1012 (2009). doi:http://dx.doi.org/10.1016/j.jclinepi.2009.06.005
12. Hoy, D., Brooks, P., Woolf, A., Blyth, F., March, L., Bain, C., Baker, P., Smith, E., Buchbinder, R.: Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J. Clin. Epidemiol. **65**(9), 934-939 (2012). doi: 10.1016/j.jclinepi.2011.11.014
13. Sterne, J.A.C., Gavaghan, D., Egger, M.: Publication and related bias in meta-analysis: Power of statistical tests and prevalence in the literature. J. Clin. Epidemiol. **53**(11), 1119-1129 (2000). doi:10.1016/s0895-4356(00)00242-0
14. Peters, J.L., Sutton, A.J., Jones, D.R., Abrams, K.R., Rushton, L., Moreno, S.G.: Assessing publication bias in meta-analyses in the presence of between-study heterogeneity. J. R. Stat. Soc. Ser. A-Stat. Soc. **173**(3), 575-591 (2010). doi:10.1111/j.1467-985X.2009.00629.x
15. Kanis, J.A., Melton, L.J., Christiansen, C., Johnston, C.C., Khaltaev, N.: The diagnosis of osteoporosis. J. Bone Miner. Res. **9**(8), 1137-1141 (1994). doi:10.1002/jbmr.5650090802
16. Takkouche, B., Cadarso-Suárez, C., Spiegelman, D.: Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. Am. J. Epidemiol. **150**(2), 206-215 (1999).
17. Dersimonian, R.: Meta-analysis in the design and monitoring of clinical trials. Stat. Med. **15**(12), 1237-1248 (1996). doi:10.1002/(sici)1097-0258(19960630)15:12<1237::aid-sim301>3.0.co;2-n
18. Doi, S.A., Thalib, L.: A quality-effects model for meta-analysis. Epidemiology 19(1), 94-100 (2008). doi:10.1097/EDE.0b013e31815c24e7
19. Doi, S.A.R., Barendregt, J.J., Mozurkewich, E.L.: Meta-analysis of heterogeneous clinical trials: an empirical example. Contemp. Clin. Trials **32**(2), 288-298 (2011). doi:http://dx.doi.org/10.1016/j.cct.2010.12.006
20. Senn, S.: Trying to be precise about vagueness. Stat. Med. **26**(7), 1417-1430 (2007). doi:10.1002/sim.2639
21. Sieber, P.R., Rommel, F.M., Theodoran, C.G., Russinko, P.J., Woodward, C.A., Schimke, L.: The role of distal third radius dual energy X-ray absorptiometry (DXA) and central DXA in evaluating for osteopenia and osteoporosis in men receiving androgen

deprivation therapy for prostate cancer. J. Clin. Densitom. **15**(3), 351-354 (2012). doi:10.1016/j.jocd.2012.01.010
22. Yu, E.Y., Kuo, K.F., Gulati, R., Chen, S., Gambol, T.E., Hall, S.P., Jiang, P.Y., Pitzel, P., Higano, C.S.: Long-term dynamics of bone mineral density during intermittent androgen deprivation for men with nonmetastatic, hormone-sensitive prostate cancer. J. Clin. Oncol. **30**(15), 1864-1870 (2012). doi:10.1200/jco.2011.38.3745
23. Wang, W., Yuasa, T., Tsuchiya, N., Maita, S., Kumazawa, T., Inoue, T., Saito, M., Ma, Z., Obara, T., Tsuruta, H., Satoh, S., Habuchi, T.: Bone mineral density in Japanese prostate cancer patients under androgen-deprivation therapy. Endocr.-Relat. Cancer **15**(4), 943-952 (2008). doi:10.1677/erc-08-0116
24. Yuasa, T., Maita, S., Tsuchiya, N., Takahashi, S., Hatake, K., Fukui, I., Habuchi, T.: Relationship between bone mineral density and androgen-deprivation therapy in Japanese prostate cancer patients. J. Urol. **183**(4), e335 (2010). doi:10.1016/j.urology.2009.10.075
25. Deng, J.H., Yang, L.P., Wang, L.S., Zhou, D.F.: Effect of androgen deprivation therapy on bone mineral density in prostate cancer patients. Asian J. Androl. **6**(1), 75-77 (2004).
26. Spry, N.A., Galvao, D.A., Davies, R., La Bianca, S., Joseph, D., Davidson, A., Prince, R.: Long-term effects of intermittent androgen suppression on testosterone recovery and bone mineral density: results of a 33-month observational study. BJU Int. **104**(6), 806-812 (2009). doi:10.1111/j.1464-410X.2009.08458.x
27. Bruder, J.M., Ma, J.Z., Basler, J.W., Welch, M.D.: Prevalence of osteopenia and osteoporosis by central and peripheral bone mineral density in men with prostate cancer during androgen-deprivation therapy. Urology **67**(1), 152-155 (2006). doi:10.1016/j.urology.2005.07.017
28. Chen, Z., Maricic, M., Nguyen, P., Ahmann, F.R., Bruhn, R., Dalkin, B.L.: Low bone density and high percentage of body fat among men who were treated with androgen deprivation therapy for prostate carcinoma. Cancer **95**(10), 2136-2144 (2002). doi:10.1002/cncr.10967
29. Wei, J.T., Gross, M., Jaffe, C.A., Gravlin, K., Lahaie, M., Faerber, G.J., Cooney, K.A.: Androgen deprivation therapy for prostate cancer results in significant loss of bone density. Urology **54**(4), 607-611 (1999). doi:10.1016/S0090-4295(99)00301-5
30. Bernat, M.M., Pasini, J., Marekovic, Z.: Changes in bone mineral density in patients with prostate cancer treated with androgen deprivation therapy. Coll. Antropol. **29**(2), 589-591 (2005).
31. Morote, J., Morin, J.P., Orsola, A., Abascal, J.M., Salvador, C., Trilla, E., Raventos, C.X., Cecchini, L., Encabo, G., Reventos, J.: Prevalence of osteoporosis during long-term

androgen deprivation therapy in patients with prostate cancer. Urology **69**(3), 500-504 (2007). doi:10.1016/j.urology.2006.11.002
32. Peters, J.L., Fairney, A., Kyd, P., Patel, A., Rogers, S., Webster, J.J., Vale, J.A., Witherow, R.O.N.: Bone loss associated with the use of LHRH agonists in prostate cancer. Prostate Cancer Prostatic Dis. 4(3), 161-166 (2001). doi:10.1038/sj.pcan.4500520
33. Planas, J., Morote, J., Orsola, A., Salvador, C., Trilla, E., Cecchini, L., Raventos, C.X., Morin, J.P.: The relationship between daily calcium intake and bone mineral density in men with prostate cancer. BJU Int. **99**(4), 812-815 (2007). doi:10.1111/j.1464-410X.2006.06695.x
34. Looker, A.C., Orwoll, E.S., Johnston, C.C., Lindsay, R.L., Wahner, H.W., Dunn, W.L., Calvo, M.S., Harris, T.B., Heyse, S.P.: Prevalence of low femoral bone density in older US adults from NHANES III. J. Bone Miner. Res. **12**(11), 1761-1768 (1997). doi:10.1359/jbmr.1997.12.11.1761
35. Brown, J.E., Cook, R.J., Major, P., Lipton, A., Saad, F., Smith, M., Lee, K.-A., Zheng, M., Hei, Y.-J., Coleman, R.E.: Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. J. Natl. Cancer Inst. **97**(1), 59-69 (2005). doi:10.1093/jnci/dji002
36. Taichman, R.S., Loberg, R.D., Mehra, R., Pienta, K.J.: The evolving biology and treatment of prostate cancer. J. Clin. Invest. **117**(9), 2351-2361 (2007). doi:10.1172/JCI31791
37. Logothetis, C.J., Lin, S.H.: Osteoblasts in prostate cancer metastasis to bone. Nat Rev Cancer **5**(1), 21-28 (2005). doi:10.1038/nrc1528
38. Keller, E.T., Brown, J.: Prostate cancer bone metastases promote both osteolytic and osteoblastic activity. J. Cell. Biochem. **91**(4), 718-729 (2004). doi:10.1002/jcb.10662
39. Coleman, R.E., Major, P., Lipton, A., Brown, J.E., Lee, K.-A., Smith, M., Saad, F., Zheng, M., Hei, Y.J., Seaman, J., Cook, R.: Predictive Value of Bone Resorption and Formation Markers in Cancer Patients With Bone Metastases Receiving the Bisphosphonate Zoledronic Acid. J. Clin. Oncol. **23**(22), 4925-4935 (2005). doi:10.1200/jco.2005.06.091
40. Rajpar, S., Massard, C., Laplanche, A., Tournay, E., Gross-Goupil, M., Loriot, Y., Di Palma, M., Bossi, A., Escudier, B., Chauchereau, A., Fizazi, K.: Urinary N-telopeptide (uNTx) is an independent prognostic factor for overall survival in patients with bone metastases from castration-resistant prostate cancer. Ann. Oncol. **21**(9), 1864-1869 (2010). doi:10.1093/annonc/mdq037

41. Krum, S.A.: Direct transcriptional targets of sex steroid hormones in bone. J. Cell. Biochem. **112**(2), 401-408 (2011). doi:10.1002/jcb.22970
42. Greenspan, S.L., Coates, P., Sereika, S.M., Nelson, J.B., Trump, D.L., Resnick, N.M.: Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J. Clin. Endocrinol. Metab. **90**(12), 6410-6417 (2005). doi:10.1210/jc.2005-0183
43. Falahati-Nini, A., Riggs, B.L., Atkinson, E.J., O'Fallon, W.M., Eastell, R., Khosla, S.: Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. J. Clin. Invest. **106**(12), 1553 (2000). doi:10.1172/JCI10942
44. Haseen, F., Murray, L., Cardwell, C., O'Sullivan, J., Cantwell, M.: The effect of androgen deprivation therapy on body composition in men with prostate cancer: systematic review and meta-analysis. J. Cancer Surviv.-Res. Pract. **4**(2), 128-139 (2010). doi:10.1007/s11764-009-0114-1
45. Alibhai, S.M.H., Gogov, S., Allibhai, Z.: Long-term side effects of androgen deprivation therapy in men with non-metastatic prostate cancer: A systematic literature review. Crit. Rev. Oncol./Hematol. **60**(3), 201-215 (2006). doi:http://dx.doi.org/10.1016/j.critrevonc.2006.06.006
46. Mittan, D., Lee, S., Miller, E., Perez, R.C., Basler, J.W., Bruder, J.M.: Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J. Clin. Endocrinol. Metab. **87**(8), 3656-3661 (2002). doi:10.1210/jc.87.8.3656
47. Hamilton, E.J., Ghasem-Zadeh, A., Gianatti, E., Lim-Joon, D., Bolton, D., Zebaze, R., Seeman, E., Zajac, J.D., Grossmann, M.: Structural decay of bone microarchitecture in men with prostate cancer treated with androgen deprivation therapy. J. Clin. Endocrinol. Metab. **95**(12), E456-E463 (2010). doi:10.1210/jc.2010-0902
48. Melton, L.J., Lieber, M.M., Atkinson, E.J., Achenbach, S.J., Zincke, H., Therneau, T.M., Khosla, S.: Fracture risk in men with prostate cancer: a population-based study. J. Bone Miner. Res. **26**(8), 1808-1815 (2011). doi:10.1002/jbmr.405
49. Smith, M.R., Lee, W.C., Brandman, J., Wang, Q., Botteman, M., Pashos, C.L.: Gonadotropin-Releasing Hormone Agonists and Fracture Risk: A Claims-Based Cohort Study of Men With Nonmetastatic Prostate Cancer. J. Clin. Oncol. **23**(31), 7897-7903 (2005). doi:10.1200/jco.2004.00.6908
50. Gatti, D., Rossini, M., Zamberlan, N., Braga, V., Fracassi, E., Adami, S.: Effect of aging on trabecular and compact bone components of proximal and ultradistal radius. Osteoporosis Int. **6**(5), 355-360 (1996). doi:10.1007/BF01623008

51. Smith, M.R., McGovern, F.J., Zietman, A.L., Fallon, M.A., Hayden, D.L., Schoenfeld, D.A., Kantoff, P.W., Finkelstein, J.S.: Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. New Engl. J. Med. **345**(13), 948-955 (2001). doi:doi:10.1056/NEJMoa010845
52. Araujo, A.B., Travison, T.G., Harris, S.S., Holick, M.F., Turner, A.K., McKinlay, J.B.: Race/ethnic differences in bone mineral density in men. Osteoporosis Int. **18**(7), 943-953 (2007). doi:10.1007/s00198-006-0321-9
53. Lewiecki, E.M., Gordon, C.M., Baim, S., Leonard, M.B., Bishop, N.J., Bianchi, M.-L., Kalkwarf, H.J., Langman, C.B., Plotkin, H., Rauch, F., Zemel, B.S., Binkley, N., Bilezikian, J.P., Kendler, D.L., Hans, D.B., Silverman, S.: International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone **43**(6), 1115-1121 (2008). doi:http://dx.doi.org/10.1016/j.bone.2008.08.106
54. Schröder, F.H., Hugosson, J., Roobol, M.J., Tammela, T.L.J., Ciatto, S., Nelen, V., Kwiatkowski, M., Lujan, M., Lilja, H., Zappa, M., Denis, L.J., Recker, F., Berenguer, A., Määttänen, L., Bangma, C.H., Aus, G., Villers, A., Rebillard, X., van der Kwast, T., Blijenberg, B.G., Moss, S.M., de Koning, H.J., Auvinen, A.: Screening and prostate-cancer mortality in a randomized european study. New Engl. J. Med. **360**(13), 1320-1328 (2009). doi:doi:10.1056/NEJMoa0810084
55. Pradhan, M.R., Mandhani, A., Chipde, S.S., Srivastava, A., Singh, M., Kapoor, R.: Bone densitometric assessment and management of fracture risk in Indian men of prostate cancer on androgen deprivation therapy: does practice pattern match the guidelines? Indian J. Urol. **28**(4), 399-404 (2012). doi:10.4103/0970-1591.105750
56. Tanvetyanon, T.: Physician practices of bone density testing and drug prescribing to prevent or treat osteoporosis during androgen deprivation therapy. Cancer **103**(2), 237-241 (2005). doi:10.1002/cncr.20766
57. Nadler, M., Alibhai, S., Catton, P., Catton, C., To, M.J., Jones, J.M.: Osteoporosis knowledge, health beliefs, and healthy bone behaviours in patients on androgen-deprivation therapy (ADT) for prostate cancer. BJU Int., **111**(8), 1301-1309 (2013). doi:10.1111/j.1464-410X.2012.11777.x
58. Alibhai, S.M., Yun, L., Cheung, A.M., Paszat, L.: Screening for osteoporosis in men receiving androgen deprivation therapy. JAMA **307**(3), 255-256 (2012).
59. National comprehensive cancer network: NCCN guidelines for prostate cancer (version 2.2013). http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (2013). Accessed 6th June 2013

60. Sinningen, K., Tsourdi, E., Rauner, M., Rachner, T., Hamann, C., Hofbauer, L.: Skeletal and extraskeletal actions of denosumab. Endocrine **42**(1), 52-62 (2012). doi:10.1007/s12020-012-9696-x
61. Adler, R.: Osteoporosis in men: recent progress. Endocrine **44**(1), 40-46 (2013). doi:10.1007/s12020-013-9880-7

1.6.2 **Prevalence of osteoporosis in prostate cancer not on ADT and survivors**

This meta-analysis is a continuation of the one presented in section 1.6.1 and compiles the evidence on the prevalence of osteoporosis in hormone-naïve men with prostate cancer. The results from this analysis were compared with the pooled prevalence of osteoporosis of men with prostate cancer on ADT (presented in the section 1.6.1). The studies in this second meta-analysis were mined to identify factors, other than ADT status, that could explain the differences observed in the prevalence of osteoporosis between the two populations.

Citation: Lassemillante AC, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors II: a meta-analysis of men not on androgen deprivation therapy. Endocrine. 2015.

Date submitted: 4th July 2014
Date accepted: 18th January 2015

Please note that the reference style for this manuscript is that appropriate for the journal.

Prevalence of osteoporosis in prostate cancer survivors II: A Meta-analysis of men not on androgen deprivation therapy.

Annie-Claude M. Lassemillante[1,2], Suhail A. R. Doi[3], John D. Hooper[2], John B. Prins[2,4,] Olivia R. L. Wright[1,2]

Affiliations:

[1] Centre for Dietetics Research (C-DIET-R), School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, QLD 4072, Australia.

[2] Mater Research Institute – University of Queensland, Kent Street, Woolloongabba, QLD 4102, Australia.

[3] Clinical Epidemiology Unit, School of Population Health, The University of Queensland, Herston. QLD 4006, Australia.

[4] The University of Queensland Diamantina Institute, The University of Queensland, Woolloongabba, QLD 4102, Australia.

Abstract

The prevalence of osteoporosis in men with prostate cancer (prostate cancer) on androgen deprivation therapy (ADT) is well documented, with up to 53% affected by this bone condition. However, there has been less emphasis on the burden of severe bone loss in men with prostate cancer but not undergoing ADT. Therefore the purpose of this meta-analysis is to compile evidence from the literature on the bone health of hormone-naïve prostate cancer patients and to compare it the bone health of men with prostate cancer on ADT. Three databases were searched for relevant literature published from 1990 January 2014. The pooled prevalence of osteoporosis, low bone mass and normal bone mass were estimated for this patient group and compared with similar subgroups from a previously published meta-analysis. The prevalence of osteoporosis varies from 4-38% in hormone-naïve prostate cancer patients, and men with more advanced disease have a higher prevalence of osteoporosis. Men with prostate cancer on ADT have poorer bone health than their hormone-naïve counterparts, but the trend towards poorer bone health with metastatic disease remains. In conclusion, it was found that men with prostate cancer experience poor bone health prior to treatment with ADT. These results suggest that all men with prostate cancer should have regular bone health monitoring, whether they commence ADT or not, in order to prevent or indeed minimise the morbidity that accompanies osteoporosis.

Introduction

Prostate cancer (prostate cancer) is highly prevalent in Western countries with strong evidence reporting on the deleterious side effects of one of its treatment modalities, notably androgen deprivation therapy (ADT) [1,2]. It is well-accepted that ADT leads to severe bone loss [2,3], but bone health management and osteoporosis screening are poorly implemented by doctors in this population [4]. Androgen deprivation therapy is not the first line treatment for prostate cancer [5] but the number of men receiving such treatment is increasing [6]. Such ADT candidates include men on active surveillance who are not currently receiving any medical or pharmacological treatments. Therefore ascertaining and managing their bone health early on the prostate cancer continuum has the potential to decrease their risk of future fractures. Adopting osteoporosis preventative behaviours, if needed, during active surveillance gives men with prostate cancer the opportunity to self-manage their overall health which may help in managing uncertainty that is common during this treatment modality [7,8]. Consequently this meta-analysis aims to synthesize evidence from the literature on the bone health, notably osteoporosis, of men with prostate cancer not on ADT. The secondary aim is to compare the bone health of these men to the bone health of men with prostate cancer on ADT thereby examining the burden of osteoporosis across the prostate cancer continuum.

Methods

A systematic review was carried out using the guidelines published by Littell et al. [9] and the PRISMA statement [10] was used to guide reporting. The meta-analysis protocol is similar to that used in a study focussing on the prevalence of osteoporosis in men with prostate cancer treated with ADT published by our group [11]. Therefore, a brief description of the methodology and its differences to the previously published protocol are given below.

Data sources and study selection

Studies, published from 1990 until January 2014, were identified through a systematic literature search of EMBASE, PUBMED and SCOPUS. The databases were searched using the respective controlled vocabulary of terms for “prostate cancer” and “osteoporosis” or “bone loss” (see Online resource material 1 for more details) except for SCOPUS. Studies were limited to those carried out in humans and published in English. The meta-analysis was limited to prospective longitudinal and cross-sectional studies involving hormone-naïve men with prostate cancer (not treated with ADT). Further

exclusions were made if studies did not differentiate between osteoporosis and low bone mass (osteopenia) among other exclusion criteria [11].

Data Extraction and Quality assessment

The data extracted were identical to that described in our previous study [11], with the addition of prostate cancer treatment plan, calcium intake and serum biomarkers representative of bone health. Each study was assessed using a methodological quality assessment checklist developed from the "Risk of bias tool" suggested by Hoy et al. [12] with a maximum score of 10.

Statistical methods

Prevalence of normal bone mass, low bone mass and osteoporosis as defined by World Health Organization (WHO) and/or the International Society for Clinical Densitometry (ISCD) osteoporosis diagnostic criteria [13,14] were the primary outcomes for this study. This prevalence was stratified into more homogenous subgroups by classifying the studies into low (<5%), moderate (8-30%) and severe (>30%) osteoporosis based on the prevalence reported within the studies. All analyses were performed using bias adjustment via the quality effects model [15,16] as the estimates from the random effects model have been shown to underestimate the statistical error [17,18] and are based on assumptions about random effects that may not be valid in practice [19]. The quality effects model does not assume bias can be quantified through quality scores. Rather it introduces a differential synthetic bias variance to improve the estimator performance. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias [20] therefore a *Doi* plot [21] was presented in addition to the funnel plot for comparison. This plot is similar to the funnel plot in that it resembles an inverted funnel when there is symmetry, but the studies define the limbs of the funnel instead of being confined within the funnel. To explain differences in bone health status within each stratum, the respective studies were mined for characteristics, other than ADT status, that could contribute to such discrepancy. The findings of this meta-analysis were directly compared with those from our meta-analysis investigating men with prostate cancer on ADT [11]. All analyses were done using MetaXL version 2.0 [22].

Results

Characteristics of the studies and participants

The systematic search generated 5812 articles, of which only 15 [23-37] met the inclusion criteria and have been discussed in this meta-analysis (see Figure 1.9).

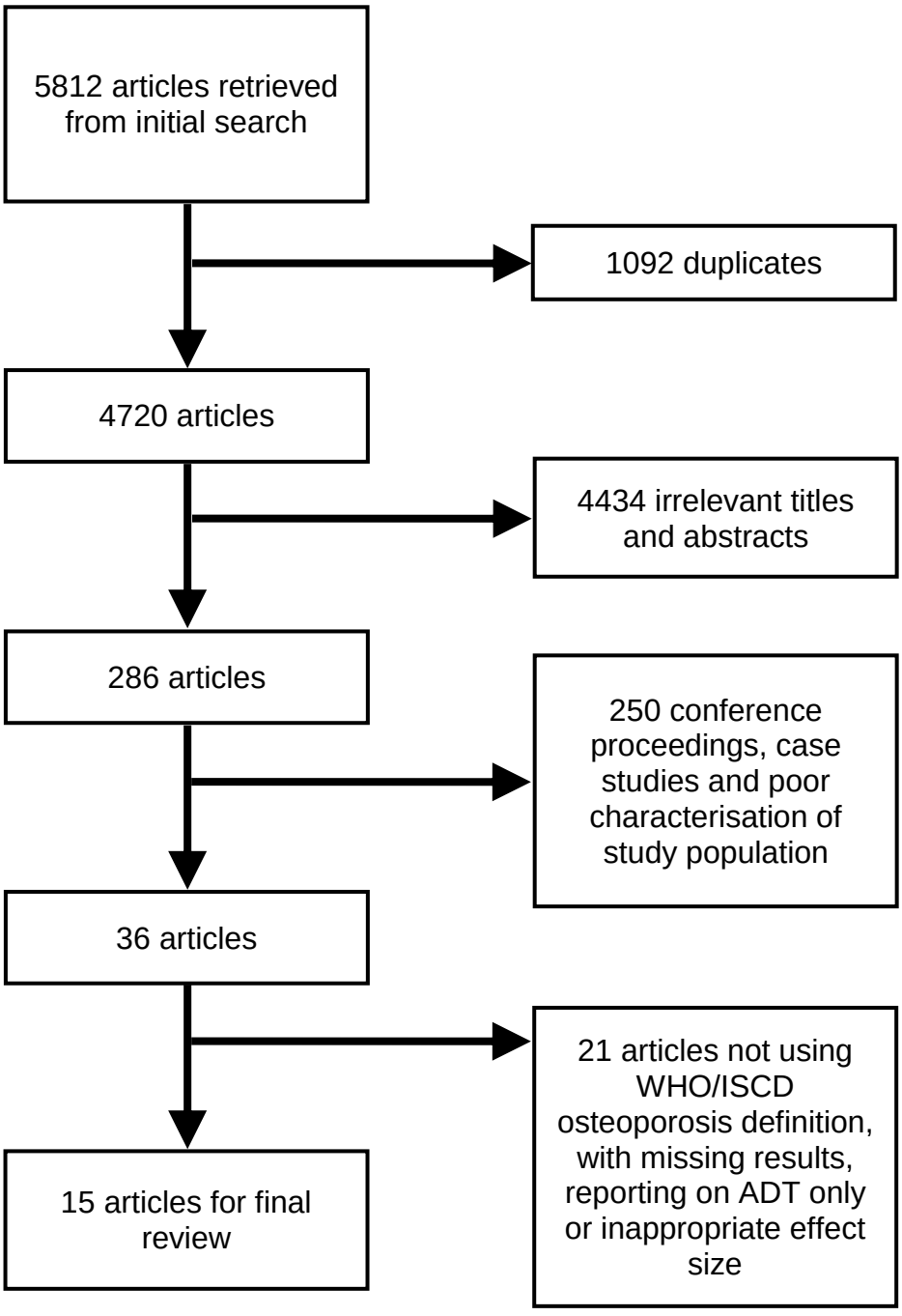


Figure 1.9 Flow diagram of study selection used in this meta-analysis.

The studies reviewed here were published between 1999 and 2013, and originated from Europe [27,30,32,33,37], USA [28,31,29], Asia [23,24,29] Canada [26,36] and Australia [35]. The total number of hormone-naïve men with prostate cancer included in this meta-analysis was 1267 (median age 69.5 years, IQR: 5.7). Nine studies [26,28,29,31-35,37] reported on men with prostate cancer eligible for ADT, and five studies [23-25,27,30]

compared the bone health of men with prostate cancer not requiring ADT, to their ADT counterparts. Alibhai et al. [36] reported on men about to commence ADT and men not eligible for ADT (separate values for age and PSA for these groups are presented in Table 1.6), with the bone health data of both groups combined in this meta-analysis. Alibhai et al. [36], Berruti et al. [32], Cheung et al. [35], Panju et al. [26], Ziaran et al. [37] and Yu et al. [28] were longitudinal studies investigating the effects of ADT on bone mineral density with baseline measurements collected prior to ADT initiation. The study by Conde et al. [31] was nested within a longitudinal ADT trial and these authors reported only on the baseline characteristics of the participants. Therefore the baseline measurements from all these studies were used in this meta-analysis.

Hussain et al. [33] were the only authors to measure bone mass at the forearm while all the other studies measured bone mass at the lumbar spine and/or hip. All the studies used dual energy x-ray absorptiometry (DXA) to measure bone mineral density and the WHO or ISCD definitions for osteoporosis. The three studies composed solely of Asian participants [23,24,29] utilised a culturally-specific normative database for determining osteoporosis status, rather than the National Health and Nutrition Examination Survey reference database that is predominantly Caucasian [38].

Disease stage was reported in all studies reviewed, with two studies [29,33] including men with metastatic disease and the rest including men with local (T_1-$T_4N_0M_0$) or locally advanced disease (T_1-$T_4N_1M_0$). Prostate cancer grade using the Gleason histological grading was reported in five studies [23,25,27,30,31], with a median score of 7 (range 6.3-7.4). Eleven studies [23-25,27,29-31,33,34,36,37] measured and reported mean or median prostate-specific antigen (PSA) levels, ranging from 0.99ng/mL to 41.4ng/mL. The mean or median PSA levels from three studies [24,30,33] could not be included here because such levels for hormone-naïve patients only could not be distinguished from the rest of the sample. The median dietary calcium intake, as reported in four studies [27,31,32,34], was 879.0mmg (range 651.3-1107.0mg). Serum calcium reported in three studies [29,33,34] ranged from 9.2mg/dL to 9.4mg/dL (2.3-2.35mmol/L). Conde et al. [31] collected vitamin D intake data via a food frequency questionnaire and found that the mean intake was 4.80±5.57µg/day (192IU/day). The respective serum vitamin D (25-hydroxyvitamin D) measured in two studies [34,35] was 22±8ng/mL and 25.24±8.81ng/mL (54.91±19.97nmol/L and 63±22nmol/L).

Quality of studies

All the studies were deemed to be at moderate risk of bias, with five studies [24,26,28,33,37] scoring the lowest as they lacked four bias protective measures. Overall the studies reviewed in this meta-analysis had flaws in external validity mostly due to poor reporting on selection criteria and narrow sampling frame. The lack of reporting on sampling data is common and has been documented before [39]. In this meta-analysis, most participants were recruited from medical centres rather than the general population, therefore allowing for more accurate reporting of primary outcome and detailed medical information. The study by Panju et al. [26] had an internal validity issue where some of the data were not collected directly from participants, although it is important to note that such flaw did not apply to bone mineral density but rather to other aspects of this study.

Comparison of bone health across two hormonally diverse prostate cancer groups

Three distinct subgroups, based on osteoporosis severity, were identified among hormone-naïve prostate cancer patients (See Table 1.7). Five studies reported a low prevalence of osteoporosis [23,25,26,28,34], with a pooled prevalence of 3.9% (95% CI: 0.7%-9.1%) and seven studies reported a moderate prevalence of osteoporosis [24,29,31,32,35-37] (pooled prevalence 12.6%, 95% CI: 7.8%-18.1%). The remaining three studies [27,30,33] reported osteoporosis in more than one-third of the participants (pooled prevalence 37.8%, 95% CI: 31.5%-44.4%). A comparison of these three subgroups with similar subgroups identified in a previously published meta-analysis on prostate cancer patients treated with ADT [11] is presented in Table 1.7. Seven studies [26,31-36] included here were not included in our previous meta-analysis as these either (i) did not meet the inclusion criteria [26,31-34] or (ii) were published after our first meta-analysis [35,36]. We conducted our meta-analysis both with and without these seven studies to determine whether their inclusion affected the results. Since their inclusion did not affect to the pooled prevalence of normal bone mass, osteopenia or osteoporosis, we included them for all subsequent analyses.

Overall, hormone-naïve prostate cancer patients have better bone health than their ADT treated counterparts. Table 1.7 outlines heterogeneity in the prevalence of osteoporosis in hormone-naïve prostate cancer patients similar to that of prostate cancer patients on ADT.

Low osteoporosis prevalence: defining characteristics other than hormone status
Hormone-naïve prostate cancer patients in this subgroup were younger (median 68 years, IQR: 4.6) than the men with prostate cancer on ADT (median 71.0 years, IQR: 5.7). The inclusion criteria based on prostate cancer stage varied within the studies of both hormone status groups. The majority of men in the ADT group (about 95%) appeared to be diagnosed with metastatic prostate cancer compared with none in the hormone-naïve group. While median prostate cancer aggressiveness was similar between the two patient groups, studies investigating men treated with ADT also included patients with more aggressive disease (Gleason score 7.4-8.1 v/s Gleason score 7.2-7.4).

Moderate osteoporosis prevalence: defining characteristics other than hormone status
The prevalence of osteoporosis and normal bone mass was significantly different between the two groups of men with prostate cancer (see Table 1.7). Ethnicity was heterogeneous in the hormone-naïve group, while the ADT group mostly comprised Caucasian males. The trend in age was similar to the previous osteoporosis subgroup, but the hormone-naïve prostate cancer patients included here were older than the other two subgroups (median 71 years, IQR: 5.9 versus median 68 years, IQR: 4.6 and 68.9 years, IQR: 7.6). Disease stage and grade could not be ascertained in the studies included here.

High osteoporosis prevalence: defining characteristics other than hormone status
The age trend observed here was similar to the low osteoporosis subgroup (ADT median age 71 years, IQR: 1.95; No ADT median age 68.9 years, IQR: 7.6). Around half of the hormone-naïve men were of Mediterranean descent (56.9%) compared with almost 90% of men on ADT. Additionally, all of the men on ADT had metastatic disease and moderately to highly aggressive prostate cancer, whereas 32.7% hormone-naïve had suspected metastases and intermediate aggressive disease (Gleason score 6.3-6.8).

Table 1.6 Details and characteristics of studies included in this meta-analysis.

Study name (Country)	Number of hormone-naïve patients (Recruitment year, Ethnicity)	Study design	Hormone-naïve prostate cancer patient description Age (mean±SD or median [range])* Disease stage/grade PSA level (mean ±SD or median (range))*	Prevalence of osteoporosis and low bone mass (%)	Exclusion criteria	Types of treatments received	Quality score
Yuasa, Maita et al. 2010 [23] (Japan)	88 (2006-2009, Asian)	Cross-sectional	65.1±9.7 years Gleason 7.4±1.2 PSA 12.6±10.3ng/mL	Osteoporosis 4.5% Low bone mass 29.5%	Presence of bone metastases at hip or lumbar spine	None specified	7
Deng, Yang et al. 2004 [24] (Taipei)	21 (1999-2002, Asian)	Cross-sectional	71 years (65-83 years) Stage C or D (Whitmore-Jewett Staging system Mean/median PSA level could not be determined	Osteoporosis 28.6% Low bone mass 33.3%	Secondary cause of osteoporosis, drugs affecting bone metabolism	Participants due to commence ADT	6
Wang, Yuasa et al. 2008 [25] (Japan)	43 (2006-2007, Asian)	Cross-sectional	68.1±7.3 years Gleason 7.2±1.2 PSA 10.3±24.2ng/mL	Osteoporosis 2.3% Low bone mass 44.1%	Presence of bone metastases at hip or lumbar spine	None specified	7
Panju, Breunis et al. 2009 [26] (Canada)	66 (Caucasian)	Prospective longitudinal	70.6 years Non-metastatic disease No details on PSA level	Osteoporosis 4.5% Low bone mass 50.3%	Prior ADT treatment, presence of metastases	Participants due to commence ADT	6
Planas, Morote et al. 2007 [27] (Spain)	106 (Mediterranean)	Cross-sectional	67 years (54.-80 years) Localized disease only and Gleason 6.3 PSA 7.8ng/mL (2.9-13.2 ng/mL)	Osteoporosis 34.9% Low bone mass 47.2%	Presence of bone metastases, secondary causes of osteoporosis	Radical prostatectomy	7
Yu, Kuo et al. 2012 [28] (USA)	56 (1996-2006, mostly Caucasian)	Prospective trial	64.5years (49.8- 80.9 years) Stage A2-D1 (American Urological Association system) No details on PSA level	Osteoporosis 17.9% Low bone mass 33.4%	Presence of bone metastases, prior bisphosphonates treatment, no DXA scan at baseline	Participants due to commence intermittent-ADT GnRH agonists	6

						and non-steroidal anti-androgens (initiated 2 weeks prior to GnRH agonists). This cycle re-initiated upon disease progression.	
Wei, Gross et al. 1999 [29] (USA)	8 (Caucasian and African American)	Cross-sectional	76 years (75-78 years) All participants with metastases PSA 41.4±32.4ng/mL	Osteoporosis 25.0% Low bone mass 37.5%	Documented secondary cause of osteoporosis, drugs affecting bone metabolism	Participants due to commence ADT	7
Morote, Morin et al. 2007 [30] (Spain)	124 (Mediterranean)	Cross-sectional	68.9±7.3 years Gleason 6.8±1.6 Mean/median PSA level could not be determined	Osteoporosis 35.5% Low bone mass 45.2%	Prior radiotherapy, presence of bone metastases, treatment with drugs affecting bone metabolism	Radical prostatectomy	7
Conde, Sarna et al. 2004 [31] (USA)	34 (mostly African American)	Cross-sectional (Nested within a prospective longitudinal trial)	69.1±7.6 years T1NxM0-T3NxM0 and Gleason 6.3±1.3 PSA 15.5±11.7ng/mL	Osteoporosis 17.6 % Low bone mass 57.9%	Presence of bone metastases, prior treatment with ADT or chemotherapy, documented secondary cause of osteoporosis, drugs affecting bone metabolism	Participants due to commence ADT or on watchful waiting	7
Berruti, Dogliotti et al. 2002 [32] (Italy)	35 (Mediterranean)	Longitudinal	75 years (60-85 years) T2N0/N1 and T3N0/N1 No details on PSA level	Osteoporosis 14.3% Low bone mass 45.7%	Presence of bone metastases, documented secondary causes of osteoporosis, prior treatment with bisphosphonates and other drugs known to	Participants due to commence ADT	7

					affect bone metabolism		
Hussain, Weston et al. 2003 [33] (UK)	174 (1999-2002, Caucasian)	Cross-sectional	74.6 years T1-T4 and M0-Mx Mean/median PSA could not be determined (PSA range 0.4-2148)	Osteoporosis 42.0% Low bone mass 36.8%	Prior treatment with ADT	Participants due to commence ADT	6
Smith, McGovern et al. 2001 [34] (USA)	41 (mostly Caucasian)	Cross-sectional	68±9 years Locally advanced and/or lymph node positive or recurrent disease PSA 15±21ng/mL	Osteoporosis 4.9% Low bone mass 29.3%	Presence of bone metastases, documented secondary causes of osteoporosis, prior treatment with bisphosphonates and other drugs known to affect bone metabolism	Participants due to commence ADT	7
Cheung, Pattison et al. 2013 [35] (Australia)	216 (2007-2011, Ethnicity not specified)	Longitudinal	69.8±7.1 years Non-metastatic disease No details on PSA level	Osteoporosis 10.6% Low bone mass 39.8%	Presence of bone metastases	Participants due to commence ADT	7
Alibhai, Mohamedali et al. 2013 [36] (Canada)	160 (Ethnicity not specified)	Longitudinal	69.1±6.7 years and 69.8±6.7 years[#] T1NxM0-T3NxM0 PSA 10.0 ng/mL (5.7-21.4 ng/mL) and 0.99 ng/mL (<0.05-4.5 ng/mL) [#]	Osteoporosis 8.1% Low bone mass 52.5%	Not proficient in English, presence of another malignancy, life expectancy <1 year, major neuropsychiatric abnormality and inability to ambulate without assistance	Participants about to commence ADT and men prostate cancer not eligible for ADT	7
Ziaran, Goncalves et al. 2013 [37] (Slovakia)	95 (Caucasian)	Longitudinal	73.5±6.3 years cT3a PSA 15.4±7.5 ng/mL	Osteoporosis 18.9% Low bone mass 41.1%	Presence of bone metastases, prior treatment with ADT or chemotherapy, drugs affecting bone metabolism	Participants due to commence ADT	6

*Mean or median (for age and PSA level) are presented here as reported in the studies reviewed.

#Separate results presented for men with about to commence ADT and men not eligible for ADT respectively.

Table 1.7 Results of the multi-category meta-analysis: comparing bone health status between men with prostate cancer on ADT and hormone-naïve patients.

Osteoporosis prevalence stratum	No ADT			ADT*		
	Normal bone mass	Low bone mass	Osteoporosis	Normal bone mass	Low bone mass	Osteoporosis
Low, % (95% CI)	59.5 (49.3-69.5)	36.6 (27.0-46.8)	3.9 (0.7-9.1)	46.8 (38.5-55.3)	44.6 (36.4-53.1)	8.6 (4.4-14.0)
Moderate, % (95% CI)	42.6 (35.0-50.2)	44.9 (37.2-52.5)	12.6 (7.8-18.1)	15.5 (10.2-21.7)	51.7 (43.8-59.6)	32.7 (25.5-40.3)
High, % (95% CI)	19.7 (14.7-25.3)	42.4 (36.0-49.1)	37.8 (31.5-44.4)	15.1 (12.2-18.2)	32.4 (28.6-36.5)	52.5 (48.5-56.8)

*Prevalence presented in this column has been published previously [11].

Sensitivity analyses

There was a trend towards increasing prevalence of osteoporosis in older studies (≤ 2004), in men aged over 70 years of age and in studies reporting on dietary calcium and/or vitamin D intakes (see Table 1.8). The only statistically significant difference, and of most clinical significance, was the increase in prevalence of osteoporosis in men with metastatic disease compared with those with localized or locally advanced disease (40.1%, 95% CI: 28.4-52.3% v/s 13.7%, 95% CI: 6.6-22.0%).

Publication bias

Study asymmetry was not as clear as expected using the funnel plot. The Doi plot depicted in (Figure 1.10) was slightly asymmetrical, which is indicative of a preponderance of lower prevalence studies. However, this asymmetry could also result from study heterogeneity rather than publication bias. This heterogeneity has been addressed by stratification of studies into three homogeneous subgroups by prevalence as presented above.

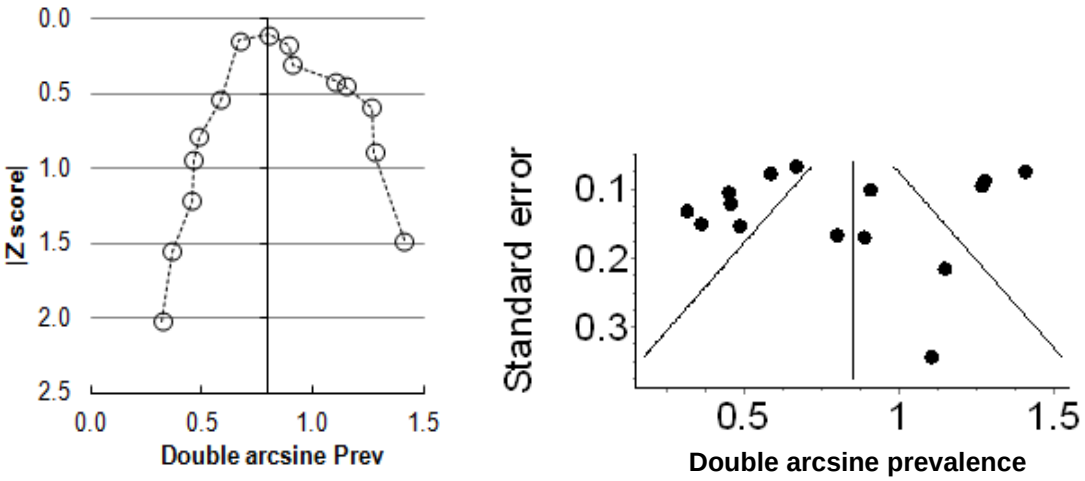


Figure 1.10 *Doi* plot (left) and funnel plot (right) to assess study asymmetry.

Discussion

Major findings

This meta-analysis is the first to compile evidence on the prevalence of osteoporosis in hormone-naïve men with prostate cancer. Significant bone loss is experienced by 80% of hormone-naïve men with prostate cancer, of whom 3.9-37.8% have osteoporosis. This prevalence is lower than that of men with prostate cancer on ADT (9.0-53.0%) [11], but higher than that of healthy older males (6-10%) [38,40]. A study investigating advanced prostate cancer prior to ADT [33], which is included in this meta-analysis, reported similar

prevalence figures to our high prevalence group. The prostate cancer-free age-matched controls included in this study also had prevalence figures comparable with our moderate prevalence group. This suggests that advanced prostate cancer itself serves as a risk factor for osteoporosis independent of ADT or age. This is not surprising since prostate cancer with skeletal metastases is associated with increased bone resorption [41,42] as illustrated by elevated markers of bone resorption when compared with localized prostate cancer or benign prostatic hyperplasia [43]. This supports the findings from our sensitivity analysis that showed a three-fold increase in the prevalence of osteoporosis in hormone-naïve men with metastatic prostate cancer compared to those with localized or locally advanced disease. While increased bone resorption clearly occurs in advanced metastatic prostate cancer, its mechanism is less clear. One possible contributing factor is the osteoblastic metastases [44-47] driving the mild hyperparathyroidism seen in men with prostate cancer [48]. This may lead to parathyroid hormone-driven systemic osteoclastic bone resorption to restore the bone/serum calcium equilibrium [49]. Regardless of the putative mechanism, it seems clear that in clinical practice, metastatic status can be used in the decision-making process about bone health management.

The prevalence of osteoporosis in the moderate prevalence subgroup, which did not include men with metastatic prostate cancer, may reflect the burden of age or of additional prostate cancer related radiation therapy [50]. The latter leads to some degree of hypogonadism [51,52], probably due to testicular damage [53]. This decline in testosterone is seen in the year following radiation therapy to the prostate [52] but has also been found to persist three to eight years post-radiation [51]. Such low levels of androgens are likely to affect bone health similarly to ADT but the rate of bone loss may not be as rapid. The interplay between a greater burden of such treatment and of age may explain the difference in prevalence of osteoporosis in our moderate prevalence group compared with our low prevalence group.

Table 1.8 Sensitivity analyses in studies investigating osteoporosis in hormone-naïve men with prostate cancer.

Studies selected if	Normal bone mass prevalence, % (95 % CI)	Low bone mass prevalence, % (95% CI)	Osteoporosis prevalence, % (95% CI)
Publication year			
>2004	42.2 (28.6-53.9)	44.3 (30.5-56.1)	13.5 (5.5-23.2)
≤ 2004	32.7 (12.7-53.8)	40.0 (18.2-61.1)	27.3 (8.9-48.1)
Reporting of dietary calcium and/or vitamin D intake			
Yes	31.6 (8.5-56.9)	46.8 (19.3-71.3)	21.6 (2.9-46.0)
No	41.8 (27.0-54.6)	42.8 (27.9-55.6)	15.4 (6.1-26.5)
ADT focus of research*			
Yes	42.1 (28.0-54.9)	43.2 (29.0-55.9)	14.7 (5.9-25.3)
No	34.6 (9.0-60.4)	44.4 (15.5-69.4)	21.0 (1.8-46.2)
Median age			
<70yrs	42.8 (26.9-56.7)	43.8 (27.8-57.7)	13.3 (4.2-24.9)
≥70yrs	33.0 (14.4-52.3)	42.3 (21.7-61.6)	24.7 (8.5-43.5)
Disease stage			
Localized or locally advanced disease only	42.4 (30.6-52.6)	43.9 (32.0-54.1)	13.7[#] (6.6-22.0)
Metastatic disease	23.0 (13.4-34.0)	36.9 (25.5-49.0)	40.1[#] (28.4-52.3)

*Although ADT was the focus of these studies, only data on controls or prior to ADT initiation have been included here; [#]These values are statistically different.

Implications in the monitoring of bone health in the prostate cancer patient

Androgen deprivation therapy has been associated with higher fracture risks in men with prostate cancer [54], but there is increasing evidence suggesting poor implementation of bone health monitoring and management in men with prostate cancer initiating ADT [55]. This meta-analysis reveals that the majority of men who are potential ADT candidates already have low bone mass or osteoporosis. We concluded that these patients did not meet their calcium requirements (879.0 mg/day against RDA 1000-1200mg [56]), nor did they meet their vitamin D requirements (192 IU/day against RDA 600-800IU [56]), and some of them were vitamin D insufficient based on the Endocrine Society Vitamin D insufficiency definition [57]. Therefore these patients are at even greater risk of

pathological fractures, upon treatment initiation, due to baseline elevated fracture risks. As a result, osteoporosis preventative strategies and/or pharmacological management will likely come too late in delaying pathological fractures. It is recommended that newly diagnosed men with prostate cancer be educated about osteoporosis preventative behaviours such as increasing calcium and vitamin D intake (via diet alone or supplements) and weight bearing exercise [58]. The timing of DXA scanning in men with prostate cancer on ADT differs internationally [5,59,60], but it may be useful to scan prostate cancer patients at baseline and 1-2 yearly thereafter [61] to identify whether pharmacological management is needed even before ADT. The WHO-endorsed fracture assessment tool, FRAX [62,63], should also be used prior to ADT initiation to determine the treatment plan [5]. While this tool can still be used once ADT has started, and is recommended by National Osteoporosis Foundation [62,63] and National Comprehensive Cancer Network [5], it may underestimate fracture risk in men with prostate cancer on ADT [64,65]. The FRAX tool does not take into account the increase in fracture risk with increasing duration of ADT [54]. Clinical judgment is paramount when managing bone health in prostate cancer patients, regardless of hormone status, hence awareness of the magnitude of poor bone health in this population is essential.

Limitations and conclusion

This meta-analysis aims at informing health professionals on the burden of osteoporosis in hormone-naïve men with prostate cancer, who are potential ADT candidates. The level of detail included in the studies reviewed by us dictated the information presented in this meta-analysis. We note that additional clinical data may have been valuable in assisting the understanding of heterogeneity in the prevalence of osteoporosis. For example, the potential impact of some clinically relevant treatments, such as radiation therapy, could not be explored here, and this represents a limitation of this meta-analysis.

In conclusion, it has been found that hormone-naïve men with prostate cancer and potential ADT candidates have a high prevalence of low bone mass and osteoporosis but these remain lower than those of men with prostate cancer on ADT. This reinforces the idea that osteoporosis also affects men, but more importantly affects a sub-population which is at potential risk of increased pathological fractures. The disastrous resulting effects, notably fractures, therefore call for changes in the management of bone health in men with prostate cancer. A multidisciplinary approach is essential to reduce the added workload on the treating physician.

References

1. Higano, C.S.: Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. Urology 61(2, Supplement), 32-38 (2003). doi:http://dx.doi.org/10.1016/S0090-4295(02)02397-X

2. Taylor, L.G., Canfield, S.E., Du, X.L.: Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. Cancer 115(11), 2388-2399 (2009). doi:10.1002/cncr.24283

3. Greenspan, S.L., Coates, P., Sereika, S.M., Nelson, J.B., Trump, D.L., Resnick, N.M.: Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J. Clin. Endocrinol. Metab. 90(12), 6410-6417 (2005). doi:10.1210/jc.2005-0183

4. Alibhai, S.M., Yun, L., Cheung, A.M., Paszat, L.: Screening for osteoporosis in men receiving androgen deprivation therapy. JAMA 307(3), 255-256 (2012). doi:10.1001/jama.2011.2022.

5. National comprehensive cancer network: NCCN guidelines for prostate cancer (version 2.2014). http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (2014). Accessed 14th April 2014

6. Grossmann, M., Hamilton, E.J., Gilfillan, C., Bolton, D., Joon, D.L., Zajac, J.D.: Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy. Med. J. Aust. 194(6), 301-306 (2011).

7. Bailey, D.E., Wallace, M., Mishel, M.H.: Watching, waiting and uncertainty in prostate cancer. J. Clin. Nurs. 16(4), 734-741 (2007). doi:10.1111/j.1365-2702.2005.01545.x

8. Oliffe, J.L., Davison, B.J., Pickles, T., Mróz, L.: The Self-Management of Uncertainty Among Men Undertaking Active Surveillance for Low-Risk Prostate Cancer. Qual. Health Res. 19(4), 432-443 (2009). doi:10.1177/1049732309332692

9. Littell, J.H., Corcoran, J., Pillai, V.K.: Systematic reviews and meta-analysis. Pocket guides to social work research methods. Oxford University Press, (2008)

10. Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G.: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. J. Clin. Epidemiol. 62(10), 1006-1012 (2009). doi:http://dx.doi.org/10.1016/j.jclinepi.2009.06.005

11. Lassemillante, A.-C.M., Doi, S.A., Hooper, J.D., Prins, J.B., Wright, O.R.: Prevalence of osteoporosis in prostate cancer survivors: a meta-analysis. Endocrine 45(3), 370-381 (2014). doi:10.1007/s12020-013-0083-z

12. Hoy, D., Brooks, P., Woolf, A., Blyth, F., March, L., Bain, C., Baker, P., Smith, E., Buchbinder, R.: Assessing risk of bias in prevalence studies: modification of an existing

tool and evidence of interrater agreement. J. Clin. Epidemiol. 65(9), 934-939 (2012). doi: 10.1016/j.jclinepi.2011.11.014
13. Kanis, J.A., Melton, L.J., Christiansen, C., Johnston, C.C., Khaltaev, N.: The diagnosis of osteoporosis. J. Bone Miner. Res. 9(8), 1137-1141 (1994). doi:10.1002/jbmr.5650090802
14. Lewiecki, E.M., Gordon, C.M., Baim, S., Leonard, M.B., Bishop, N.J., Bianchi, M.-L., Kalkwarf, H.J., Langman, C.B., Plotkin, H., Rauch, F., Zemel, B.S., Binkley, N., Bilezikian, J.P., Kendler, D.L., Hans, D.B., Silverman, S.: International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone 43(6), 1115-1121 (2008). doi:http://dx.doi.org/10.1016/j.bone.2008.08.106
15. Doi, S.A., Thalib, L.: A quality-effects model for meta-analysis. Epidemiology 19(1), 94-100 (2008).
16. Doi, S.A.R., Barendregt, J.J., Mozurkewich, E.L.: Meta-analysis of heterogeneous clinical trials: an empirical example. Contemp. Clin. Trials 32(2), 288-298 (2011). doi:http://dx.doi.org/10.1016/j.cct.2010.12.006
17. Noma, H.: Confidence intervals for a random-effects meta-analysis based on Bartlett-type corrections. Stat. Med. 30(28), 3304-3312 (2011). doi:10.1002/sim.4350
18. Brockwell, S.E., Gordon, I.R.: A comparison of statistical methods for meta-analysis. Stat. Med. 20(6), 825-840 (2001). doi: http://dx.doi.org/10.1037/1082-989X.3.3.354
19. Overton, R.C.: A comparison of fixed-effects and mixed (random-effects) models for meta-analysis tests of moderator variable effects. Psychol. Methods 3(3), 354 (1998). doi: http://dx.doi.org/10.1037/1082-989X.3.3.354
20. Hunter, J.P., Saratzis, A., Sutton, A.J., Boucher, R.H., Sayers, R.D., Bown, M.J.: In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J. Clin. Epidemiol. 67(8), 897-903 (2014). doi:10.1016/j.jclinepi.2014.03.003
21. Onitilo, A.A., Doi, S.A.R., Barendregt, J.J.: Meta-analysis II. In: Doi, S.A.R., Williams, G.M. (eds.) Methods of Clinical Epidemiology. Springer Series on Epidemiology and Public Health, pp. 253-266. Springer Berlin Heidelberg, (2013)
22. Epigear International: MetaXL. Version 2.0 (2014)
23. Yuasa, T., Maita, S., Tsuchiya, N., Takahashi, S., Hatake, K., Fukui, I., Habuchi, T.: Relationship between bone mineral density and androgen-deprivation therapy in Japanese prostate cancer patients. J. Urol. 183(4), e335 (2010). doi: 10.1016/j.urology.2009.10.075.
24. Deng, J.H., Yang, L.P., Wang, L.S., Zhou, D.F.: Effect of androgen deprivation therapy on bone mineral density in prostate cancer patients. Asian J. Androl. 6(1), 75-77 (2004).

25. Wang, W., Yuasa, T., Tsuchiya, N., Maita, S., Kumazawa, T., Inoue, T., Saito, M., Ma, Z., Obara, T., Tsuruta, H., Satoh, S., Habuchi, T.: Bone mineral density in Japanese prostate cancer patients under androgen-deprivation therapy. Endocr. Relat. Cancer 15(4), 943-952 (2008). doi:10.1677/erc-08-0116
26. Panju, A.H., Breunis, H., Cheung, A.M., Leach, M., Fleshner, N., Warde, P., Duff-Canning, S., Krahn, M., Naglie, G., Tannock, I., Tomlinson, G., Alibhai, S.M.H.: Management of decreased bone mineral density in men starting androgen-deprivation therapy for prostate cancer. BJU Int. 103(6), 753-757 (2009). doi:10.1111/j.1464-410X.2008.08156.x
27. Planas, J., Morote, J., Orsola, A., Salvador, C., Trilla, E., Cecchini, L., Raventos, C.X., Morin, J.P.: The relationship between daily calcium intake and bone mineral density in men with prostate cancer. BJU Int. 99(4), 812-815 (2007). doi: 10.1111/j.1464-410X.2006.06695.x
28. Yu, E.Y., Kuo, K.F., Gulati, R., Chen, S., Gambol, T.E., Hall, S.P., Jiang, P.Y., Pitzel, P., Higano, C.S.: Long-term dynamics of bone mineral density during intermittent androgen deprivation for men with nonmetastatic, hormone-sensitive prostate cancer. J. Clin. Oncol. 30(15), 1864-1870 (2012). doi:10.1200/jco.2011.38.3745
29. Wei, J.T., Gross, M., Jaffe, C.A., Gravlin, K., Lahaie, M., Faerber, G.J., Cooney, K.A.: Androgen deprivation therapy for prostate cancer results in significant loss of bone density. Urology 54(4), 607-611 (1999). doi: 10.1016/S0090-4295(99)00301-5
30. Morote, J., Morin, J.P., Orsola, A., Abascal, J.M., Salvador, C., Trilla, E., Raventos, C.X., Cecchini, L., Encabo, G., Reventos, J.: Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology 69(3), 500-504 (2007). doi:10.1016/j.urology.2006.11.002
31. Conde, F.A., Sarna, L., Oka, R.K., Vredevoe, D.L., Rettig, M.B., Aronson, W.J.: Age, body mass index, and serum prostate-specific antigen correlate with bone loss in men with prostate cancer not receiving androgen deprivation therapy. Urology 64(2), 335-340 (2004). doi:10.1016/j.urology.2004.03.036
32. Berruti, A., Dogliotti, L., Terrone, C., Cerutti, S., Isaia, G., Tarabuzzi, R., Reimondo, G., Mari, M., Ardissone, P., De Luca, S., Fasolis, G., Fontana, D., Rossetti, S.R., Angeli, A., Gruppo Onco Urologico Piemontese, R.O.P.: Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J. Urol. 167(6), 2361-2367 (2002). doi: 10.1016/S0022-5347(05)64985-3

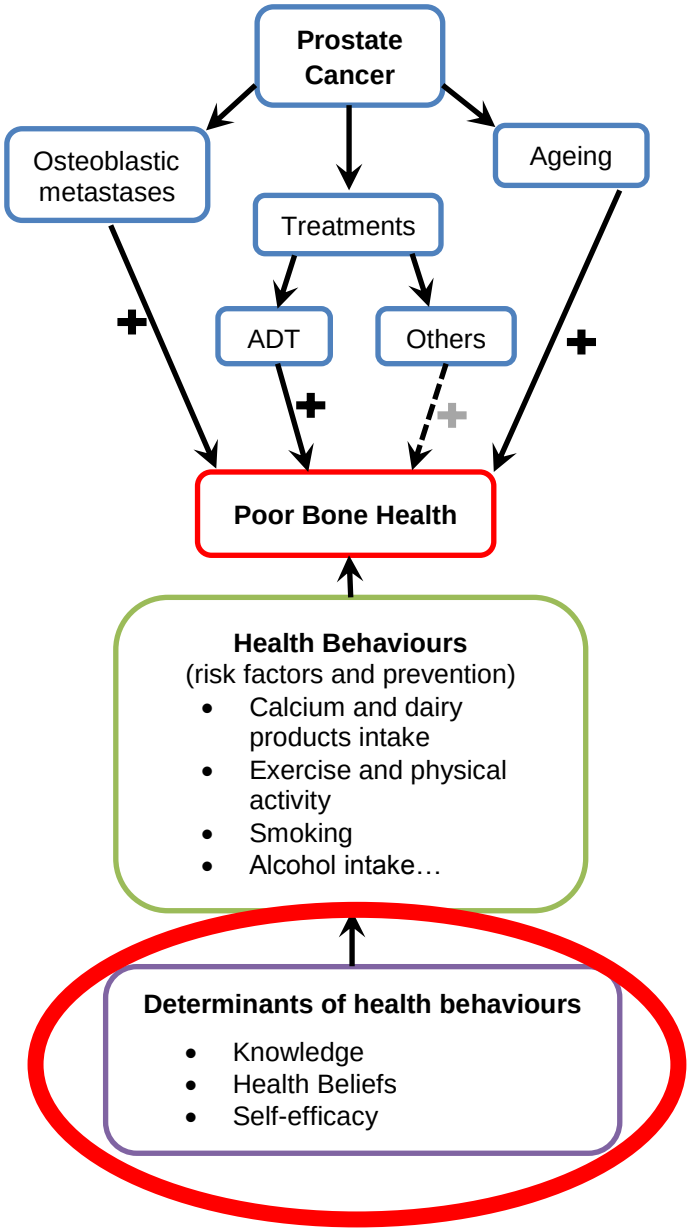
33. Hussain, S.A., Weston, R., Stephenson, R.N., George, E., Parr, N.J.: Immediate dual energy X-ray absorptiometry reveals a high incidence of osteoporosis in patients with advanced prostate cancer before hormonal manipulation. BJU Int. 92(7), 690-694 (2003). doi:10.1046/j.1464-410X.2003.04471.x
34. Smith, M.R., McGovern, F.J., Fallon, M.A., Schoenfeld, D., Kantoff, P.W., Finkelstein, J.S.: Low bone mineral density in hormone-naive men with prostate carcinoma. Cancer 91(12), 2238-2245 (2001). doi:10.1002/1097-0142(20010615)91:12<2238::AID-CNCR1254>3.0.CO;2-2
35. Cheung, A., Pattison, D., Bretherton, I., Hoermann, R., Lim Joon, D., Ho, E., Jenkins, T., Hamilton, E., Bate, K., Chan, I.: Cardiovascular risk and bone loss in men undergoing androgen deprivation therapy for non-metastatic prostate cancer: implementation of standardized management guidelines. Andrology 1(4), 583-589 (2013). doi:10.1111/j.2047-2927.2013.00093
36. Alibhai, S., Mohamedali, H., Gulamhusein, H., Panju, A., Breunis, H., Timilshina, N., Fleshner, N., Krahn, M., Naglie, G., Tannock, I.: Changes in bone mineral density in men starting androgen deprivation therapy and the protective role of vitamin D. Osteoporos. Int. 24(10), 2571-2579 (2013). doi:10.1007/s00198-013-2343-4
37. Ziaran, S., Goncalves, F.M., Sn, J.B.: Complex metabolic and skeletal changes in men taking long-term androgen deprivation therapy. Clin. Genitourin. Cancer 11(1), 33-38 (2013). doi:10.1016/j.clgc.2012.08.005
38. Looker, A.C., Orwoll, E.S., Johnston, C.C., Lindsay, R.L., Wahner, H.W., Dunn, W.L., Calvo, M.S., Harris, T.B., Heyse, S.P.: Prevalence of low femoral bone density in older US adults from NHANES III. J. Bone Miner. Res. 12(11), 1761-1768 (1997). doi:10.1359/jbmr.1997.12.11.1761
39. Demark-Wahnefried, W., Bowen, D.J., Jabson, J.M., Paskett, E.D.: Scientific Bias Arising from Sampling, Selective Recruitment, and Attrition: The Case for Improved Reporting. Cancer Epidemiol. Biomarkers Prev. 20(3), 415-418 (2011). doi:10.1158/1055-9965.epi-10-1169
40. Nguyen, T.V., Center, J.R., Eisman, J.A.: Osteoporosis in Elderly Men and Women: Effects of Dietary Calcium, Physical Activity, and Body Mass Index. J. Bone Miner. Res. 15(2), 322-331 (2000). doi:10.1359/jbmr.2000.15.2.322
41. Percival, R.C., Urwin, G.H., Harris, S., Yates, A.J., Williams, J.L., Beneton, M., Kanis, J.A.: Biochemical and histological evidence that carcinoma of the prostate is associated with increased bone resorption. Eur. J. Surg. Oncol. 13(1), 41-49 (1987).

42. Urwin, G.H., Percival, R.C., Harris, S., Beneton, M.N., Williams, J.L., Kanis, J.A.: Generalised increase in bone resorption in carcinoma of the prostate. Br. J. Urol. 57(6), 721-723 (1985). doi: 10.1111/j.1464-410X.1985.tb07040.x
43. Garnero, P., Buchs, N., Zekri, J., Rizzoli, R., Coleman, R.E., Delmas, P.D.: Markers of bone turnover for the management of patients with bone metastases from prostate cancer. Br. J. Cancer 82(4), 858-864 (2000). doi:10.1054/bjoc.1999.1012
44. Guise, T.A., Mundy, G.R.: Cancer and Bone. Endocr. Rev. 19(1), 18-54 (1998). doi:doi:10.1210/edrv.19.1.0323
45. Diamond, T.H., Higano, C.S., Smith, M.R., Guise, T.A., Singer, F.R.: Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy. Cancer 100(5), 892-899 (2004). doi:10.1002/cncr.20056
46. Logothetis, C.J., Lin, S.H.: Osteoblasts in prostate cancer metastasis to bone. Nat. Rev. Cancer 5(1), 21-28 (2005). doi: 10.1038/nrc1528
47. Weilbaecher, K.N., Guise, T.A., McCauley, L.K.: Cancer to bone: a fatal attraction. Nat. Rev. Cancer 11(6), 411-425 (2011). doi: 10.1038/nrc3055
48. Murray, R., Grill, V., Crinis, N., Ho, P., Davison, J., Pitt, P.: Hypocalcemic and normocalcemic hyperparathyroidism in patients with advanced prostatic cancer. J. Clin. Endocrinol. Metab. 86(9), 4133-4138 (2001).
49. DiGirolamo, D.J., Clemens, T.L., Kousteni, S.: The skeleton as an endocrine organ. Nat. Rev. Rheumatol. 8(11), 674-683 (2012). doi:10.1038/nrrheum.2012.157
50. Reuss-Borst, M., Hartmann, U., Scheede, C., Weiß, J.: Prevalence of osteoporosis among cancer patients in Germany. Osteoporos. Int. 23(4), 1437-1444 (2012). doi:10.1007/s00198-011-1724-9
51. Daniell, H.W., Clark, J.C., Pereira, S.E., Niazi, Z.A., Ferguson, D.W., Dunn, S.R., Figueroa, M.L., Stratte, P.T.: Hypogonadism following prostate-bed radiation therapy for prostate carcinoma. Cancer 91(10), 1889-1895 (2001). doi:10.1002/1097-0142(20010515)91:10<1889::AID-CNCR1211>3.0.CO;2-U
52. Pickles, T.O.M., Graham, P.: What Happens to Testosterone After Prostate Radiation Monotherapy And Does it Matter? J. Urol. 167(6), 2448-2452 (2002). doi:http://dx.doi.org/10.1016/S0022-5347(05)65002-1
53. Fiorino, C., Valdagni, R., Rancati, T., Sanguineti, G.: Dose–volume effects for normal tissues in external radiotherapy: Pelvis. Radiother. Oncol. 93(2), 153-167 (2009). doi:http://dx.doi.org/10.1016/j.radonc.2009.08.004

54. Shahinian, V.B., Kuo, Y.F., Freeman, J.L., Goodwin, J.S.: Risk of fracture after androgen deprivation for prostate cancer. N. Engl. J. Med. 352(2), 154-164 (2005). doi:10.1056/NEJMoa041943
55. Morgans, A.K., Smith, M.R., O'Malley, A.J., Keating, N.L.: Bone density testing among prostate cancer survivors treated with androgen-deprivation therapy. Cancer 119(4), 863-870 (2013). doi:10.1002/cncr.27830
56. Ross, A.C., Manson, J.E., Abrams, S.A., Aloia, J.F., Brannon, P.M., Clinton, S.K., Durazo-Arvizu, R.A., Gallagher, J.C., Gallo, R.L., Jones, G., Kovacs, C.S., Mayne, S.T., Rosen, C.J., Shapses, S.A.: The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. J. Clin. Endocr. Metab. 96(1), 53-58 (2011). doi:10.1210/jc.2010-2704
57. Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., Murad, M.H., Weaver, C.M.: Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. J. Clin. Endocr. Metab. 96(7), 1911-1930 (2011). doi:doi:10.1210/jc.2011-0385
58. National Osteoporosis Foundation: Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation, Washington (2014)
59. Australian Cancer Network Management of Metastatic Prostate Cancer Working Party: Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer. In. Cancer Council Australia and Australian Cancer Network, Sydney, (2010)
60. National Collaborating Centre for Cancer: Prostate cancer: diagnosis and treatment. NICE Guidelines CG175, National Institute for Health and Care Excellence. (ed.). London (UK), (2014)
61. Rhee, H., Gunter, J.H., Heathcote, P., Ho, K., Stricker, P., Corcoran, N.M., Nelson, C.C.: Adverse Effects of Androgen Deprivation Therapy in Prostate Cancer and Their Management. BJU Int. (2014). doi:10.1111/bju.12964
62. Kanis, J.A., Oden, A., Johansson, H., Borgström, F., Ström, O., McCloskey, E.: FRAX® and its applications to clinical practice. Bone 44(5), 734-743 (2009). doi:10.1016/j.bone.2009.01.373
63. Kanis, J., Johnell, O., Odén, A., Johansson, H., McCloskey, E.: FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporos. Int. 19(4), 385-397 (2008). doi:10.1007/s00198-007-0543-5

64. Saylor, P.J., Kaufman, D.S., Michaelson, M.D., Lee, R.J., Smith, M.R.: Application of a fracture risk algorithm to men treated with androgen deprivation therapy for prostate cancer. J. Urol. 183(6), 2200-2205 (2010). doi:10.1016/j.juro.2010.02.022
65. Adler, R.A., Hastings, F.W., Petkov, V.I.: Treatment thresholds for osteoporosis in men on androgen deprivation therapy: T-score versus FRAX®. Osteoporos. Int. 21(4), 647-653 (2010). doi:10.1007/s00198-009-0984-0

1.7 Psychological determinants of health behaviours



The meta-analyses outlined the extent of the bone health problem in men with prostate cancer; however, there is evidence suggesting that DXA scanning and interventions, such as promotion of bone healthy behaviours, are poorly implemented at initiation of ADT (77). Evidence also suggests that men with prostate cancer lack basic osteoporosis knowledge and do not engage in bone healthy behaviours such as physical activity/exercise, and consuming adequate calcium and vitamin D (78). It is imperative to increase men's awareness and understanding of this bone condition in order to promote the uptake of such bone healthy behaviours. Many theoretical frameworks have been used in osteoporosis research to investigate the psycho-behavioural and psycho-social drivers of

health behaviours. To understand bone healthy behaviours in men and women, two main theories have been used namely the Health Belief Model (HBM) and the Orem's self-care deficit nursing theory.

The HBM was first introduced in the 1950s (79) and encompasses several primary concepts that predict why individuals will take action to prevent, to screen for, or to control illness conditions. Self-efficacy was not incorporated in the earlier formulations of the HBM and was added in 1988 by Rosenstock, Strecher et al. (80). The constructs of this model include susceptibility, seriousness, barriers and benefits to behaviours, cues to action, and self-efficacy (81) as outlined in Figure 1.11. According to the HBM, the likelihood of engaging in health behaviours is associated with an individual's health beliefs (82) and its constructs have been coined as "*important contributors to the explanation and prediction of individuals' health behaviours*" (83). According to the HBM in the context of osteoporosis, bone healthy behaviours are more likely to change if an individual believes in personal susceptibility to osteoporosis and, at the same time, perceives that having osteoporosis would have serious consequences. This model also recognises the perceived barriers and benefits of behavioural change.

The definition of the constructs of the HBM is as follows:

- "Perceived susceptibility" is the belief about the chances of experiencing a risk or getting a condition. For example: whether men with prostate cancer perceive to be at risk of osteoporosis and/or fractures.

- "Perceived severity" is the belief about how serious a condition and its sequelae are. For example: the perception that osteoporosis and/or fractures are serious or not.

- "Perceived benefits" is the belief in efficacy of the advised action to reduce risk or seriousness of impact. For example: whether men with prostate cancer perceive that increased physical activity and calcium intake would decrease the risks of osteoporosis and/or fractures.

- "Perceived barriers" is the belief about the tangible and psychological costs of the advised action. For example: whether men with prostate cancer identify barriers to increasing physical activity and/or calcium intake.

- "Cues to action" are the strategies to activate "readiness".

- "Self-efficacy" is the confidence in one's ability to take action. For example: how confident are men with prostate cancer in increasing physical activity and/or dietary calcium?
  Sourced from (79-81).

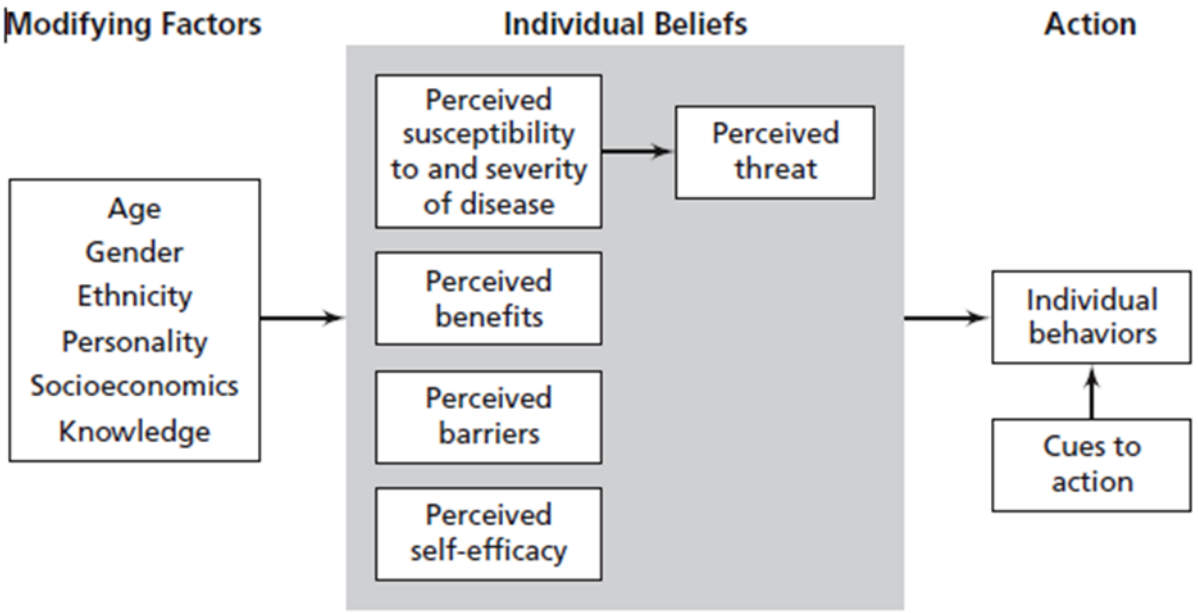


Figure 1.11 The Health Belief Model.

The constructs are highlighted in the shaded area (79-81)

Self-efficacy is derived from the social cognitive theory and has been defined as "*the conviction that one can successfully execute the behaviour required to produce the outcomes*" (84). An individual is motivated to engage in a behaviour based on the belief that it will result in a favourable outcome (outcome expectation) and on the capacity to execute the behaviour (efficacy expectation). This capacity is related to behaviour by the conviction that an individual has the ability to initiate the activity, maintain it, and persist in the activity despite obstacles (85).

Another psychological determinant of health behaviours that has been researched, especially among women, is osteoporosis knowledge (86). Knowledge falls under Orem's Self-Care Deficit Nursing Theory, which is one aspect of the Self-Care Theory (87). Self-care is defined as:

"the practice of activities that mature and maturing persons initiate and perform, within time frames, on their own behalf in the interests of maintaining life, healthful functioning, and development" (88).

Knowledge is an important aspect of chronic health awareness efforts as it informs decisions about health practices (86). In chronic disease management, increased knowledge leads to improved patient's compliance through increased identification and awareness with the decision-making process (89). Disease knowledge, especially symptom knowledge is important as it can facilitate early detection of disease (90).

Health beliefs, self-efficacy, and osteoporosis knowledge are modifiable, therefore they are important to take into consideration when designing osteoporosis interventions (91). There is still much work to do in bone health education because women are more likely to perceive themselves at risk of osteoporosis and perceive more benefits of calcium intake than men (83). This is a concern as perceived susceptibility is one of the most influential HBM construct on health behaviour (92). It was demonstrated that women were more likely to take calcium supplements if they perceived themselves at risk/susceptible to osteoporosis and if they perceived the benefits of taking calcium (83). The body of literature on these psycho-behavioural and psycho-social factors are scarce in men (83) despite the fact that osteoporosis and low bone mass are common in this gender.

1.8 Review of prostate cancer clinical guidelines: a focus on bone health management strategies

In light of the deleterious effects of ADT on bone health of men with prostate cancer, a review of the clinical guidelines for the management of prostate cancer, with a focus on bone health, was conducted. The aims were to identify the range and breadth bone health recommendations made; and to determine their relevance against the latest evidence and adequacy of translating this evidence into practice recommendations. Guidelines from the European Association of Urology (93), the UK (94), the USA (National Comprehensive Cancer Network) (3), and Australia (95) are included here. The Australian guidelines (95) for the management of advanced prostate cancer are available in a wiki format and were first published in 2010, therefore are not considered current by the NH&MRC. Although the new wiki format has allowed for some recent updates, the evidence on which the bone health recommendations are based on is at least 10 years old. Despite being outdated, these guidelines are included here as they reflect Australian evidence-based practice in

prostate cancer management up to now. The four guidelines were mined for recommendations specific to osteoporosis, bone health, and/or fractures, regardless of prostate cancer treatment. All recommendations on bone health monitoring, calcium, vitamin D, and/or exercise were appraised for their relative adequacy. Summary of such recommendations are included in Table 1.9.

The Australian clinical guidelines for the *Management of Locally Advanced and Metastatic Prostate Cancer* (95) include a comprehensive review of studies, albeit at least 10 years old, investigating bone loss secondary to ADT. This evidence (BMD loss, fractures, and frailty) is subsequently discussed in the context of ADT. The guidelines (i) recommend to consider the prostate cancer patient with his co-morbidities before prescription of ADT, and (ii) state that ADT "may not be desirable" for men with low bone mass (osteopenia). The bone health-related recommendations are Grade C, based on the NH&MRC levels of evidence and grades for recommendations, as most of the studies were observational. The guidelines recommend taking into consideration the side effects of ADT, especially osteoporosis and the increased risk of pathological fractures, before treatment is initiated. These guidelines are patient-centred as they recommend discussing the iatrogenic effects of ADT with the patients in order to tailor the treatment plan to the patient's needs. BMD monitoring is mentioned briefly as a footnote but not included in the many recommendations made in these guidelines. This footnote also includes some information about preventative strategies such as calcium and vitamin D supplementation, and exercise. In summary these guidelines offer limited recommendations on the management of bone health in the prostate cancer patient, and are inadequate in light of the extent of the osteoporosis problem exposed in sections 1.6.1 and 1.6.2.

Table 1.9 Summary of bone health-related recommendations in clinical guidelines for the management of prostate cancer

Guideline	Prescriptive in nature	Room for clinical judgement	Patient-centred	Osteoporosis and/or fractures discussed as side effects of ADT	Includes exercise recommendations	Recommends dietetic input	Calcium and vitamin D recommendations	DXA monitoring
Australian Guidelines (95)		✓	✓	✓	✓		✓ Considered to be part of clinical judgement	✓ Considered to be part of clinical judgement
EAU guidelines (93)	✓	✓		✓	✓		✓	✓
NICE guidelines (94)		✓	✓	✓	✓ For the management of fatigue not osteoporosis			
NCCN guidelines (3)	✓			✓		✓	✓	✓

NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; EAU, European Association of Urology.

The guidelines from the European Association of Urology acknowledge bone problems as systemic side effects of ADT. These guidelines promote a holistic approach, whereby the prostate cancer patient needs an overall health assessment similarly to the geriatric patient. This document also discusses the increase in bone turnover and decrease in BMD secondary to treatment with ADT. They recommend pharmacological treatment as well as encouraging patients to adopt bone healthy lifestyle changes, such as increasing physical activity, smoking cessation, reduction of alcohol intake, and normalising BMI. Calcium and vitamin D supplementation are recommended only if blood levels are low. These guidelines give detailed information on (i) how to identify patients at increased risk of fractures, including the WHO-endorsed FRAX®, and (ii) how to identify patients with behaviours that could be detrimental to their overall health. Bone health management recommendations include BMD measurement before initiation of long-term treatment, with repeated measures every year for the osteoporotic patient or very second year for the osteopenic patient. These guidelines offer a holistic and integrated approach in the management of bone health in prostate cancer patients, but the recommendations on fracture prevention need to be updated.

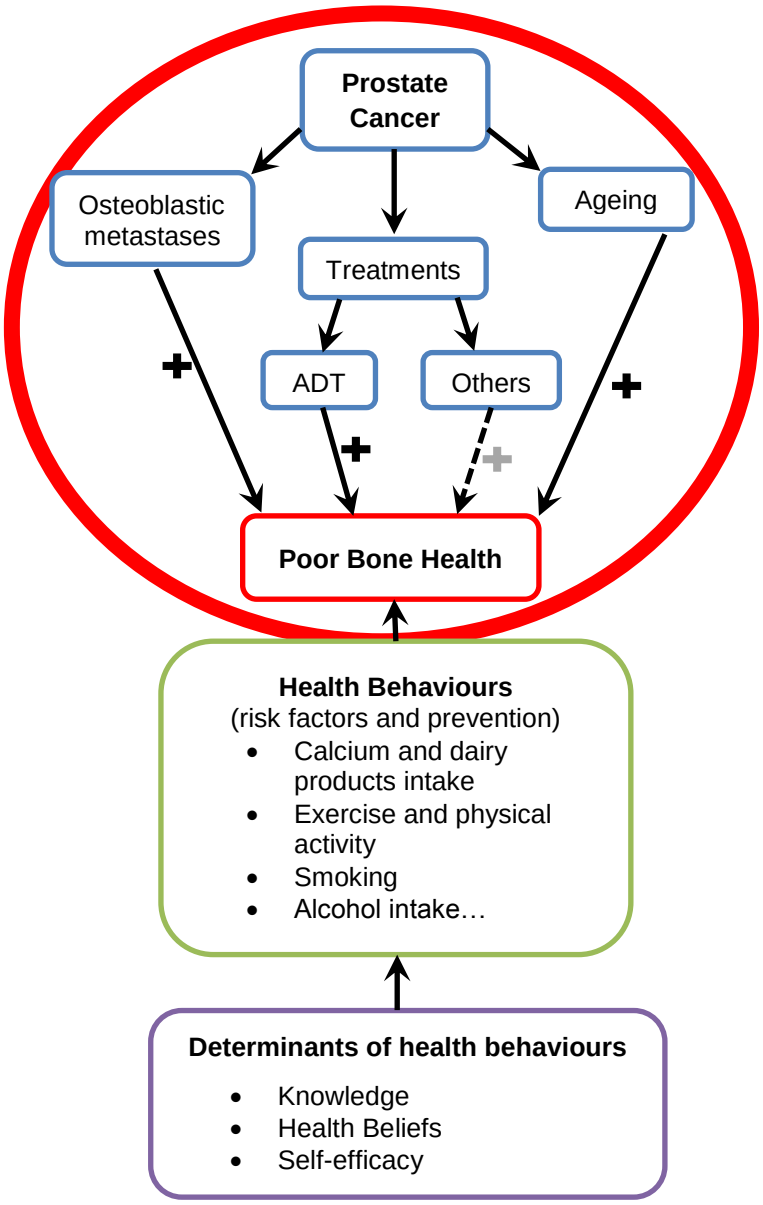
The *Prostate Cancer: Diagnosis and Treatment* guidelines from the National Institute for Health and Care Excellence (NICE) (94) were recently reviewed, with the updated version published in 2014 (previous version 2010). The discussion of the iatrogenic effects of ADT in the current guidelines is not as detailed as the other guidelines reviewed here. The updated NICE guidelines include a new, but only one, recommendation on the management of fracture risks in men with prostate cancer on ADT. Assessment of fracture risks is recommended in line with the NICE Osteoporosis guidelines; hence implying that other bone health management strategies need to be applied to this population.

The Clinical Practice Guidelines in Oncology – Prostate Cancer from the National Comprehensive Cancer Network (NCCN) (3) are the most up-to-date guidelines and provide the most comprehensive recommendations on the management of bone health in men with prostate cancer. These guidelines include a short review of the literature on prostate cancer and bone health, and the related clinical trials. All of the adverse effects of ADT are enumerated, but most of the related recommendations address osteoporosis and fractures. As with most of the prostate cancer guidelines, the NCCN recommends discussing all the side effects of ADT with the patient prior to treatment. The NCCN guidelines summarise recommendations for the screening and management of

osteoporosis, and refer to another document (from the National Osteoporosis Foundation) for further details. Fracture risk assessment is recommended using the WHO-endorsed FRAX® algorithm, with detailed instructions on how to use this algorithm in men with prostate cancer on ADT (see Appendix II for the FRAX® algorithm). Recommendations on the management of patients at increased risks of fractures, using the above-mentioned tool, are (i) supplementation with calcium (1200 mg/day) and vitamin D_3 (800 – 1000 IU/day), and (ii) following a detailed pharmacological protocol. Bone health monitoring (using DXA scanning) is recommended before treatment with ADT and one year after treatment initiation, as recommended by the ISCD. The current guidelines also acknowledge the lack of consensus on the "*optimal approach to monitor the effectiveness of drug therapy*" (meaning bone-targeted therapy). Most interestingly the NCCN guidelines are the only ones to mention the need for a nutritionist on the bone health management of men with prostate cancer. Assessment of dietary calcium intake and serum 25-hydroxy vitamin D levels should be used by this allied health professional when tailoring the bone health treatment plan.

The guidelines from the NCCN offer the most comprehensive recommendations with a strong emphasis on preventative strategies such as calcium and vitamin D supplementation; however, reviewing these four guidelines revealed a high level of inconsistency in the bone health recommendations and depth between the guidelines. Given the high prevalence of osteoporosis in men with prostate cancer, the high risk of fractures that ensues, and the strength of the evidence supporting the fracture-preventative effects of calcium and vitamin D, bone health management recommendations need to be updated. There is a clear gap between the 'gold standard' of clinical practice and bone healthy behaviours that needs to be addressed; however, it is paramount to understand current bone healthy behaviours in men with prostate cancer to better target future recommendations and interventions.

CHAPTER 2 BONE HEALTH ON THE PROSTATE CONTINUUM



The previous chapter summarised the prevalence of osteoporosis in men with prostate cancer, whether treated with ADT or not. This chapter attempts to explore the bone health of men with prostate cancer in greater details, including osteoporosis status and risk of post-diagnostic fractures, and comparing three groups of men with diseased prostates. This was achieved through the secondary analysis of DOES, from the Garvan Institute, Sydney. Data collection for this longitudinal study started in 1989 and is ongoing, with main aim to investigate the risk factors of osteoporosis in a town that was believed to be representative of the Australian population (96, 97).

The initial aim of this chapter was to identify the longitudinal changes in BMD and bone health status, starting before prostatic disease diagnosis and ending after diagnosis. This dataset comprises over 2000 men, therefore men with prostate cancer or BPH diagnosed after baseline measurement and cancer-free controls were selected for this analysis. The longitudinal changes in BMD and evolution of bone health status could not be explored due to violations of statistical assumptions, hence interfering with the reliability of the results. As a result, the focus for this manuscript evolved and aimed to investigate the effects of prostatic disease (prostate cancer and BPH) on fracture risk.

This manuscript has been submitted to The Prostate, and is currently under review.

Date submitted: 7th June 2015

Please note that the reference style for this manuscript is that appropriate for the journal.

Bone health of men with benign prostatic hyperplasia and prostate cancer

Annie-Claude M. Lassemillante[1, 2], Jacqueline R. Center[3, 4, 5], John A. Eisman[3, 4, 5, 6], Tuan V. Nguyen[3, 7, 8], John D. Hooper[2], John Prins[2, 9,] Olivia L. Wright[1, 2]

Affiliations

[1] Centre for Dietetics Research (C-DIET-R), School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, QLD 4072, Australia.

[2] Mater Research Institute – University of Queensland, Kent Street, Woolloongabba, QLD 4102, Australia.

[3] Osteoporosis and Bone Biology Program, Garvan Institute of Medical Research, Darlinghurst, NSW, 2010, Australia.

[4] Clinical School, St. Vincent's Hospital Sydney, Sydney, NSW, Australia.

[5]Faculty of Medicine, UNSW, Sydney, Australia.

[6] Clinical Translation and Advanced Education, Garvan Institute of Medical Research, and School of Medicine Sydney, University of Notre Dame Australia, Sydney, NSW, Australia

[7] UNSW School of Public Health and Community Medicine, UNSW AUSTRALIA;

[8] Centre for Health Technologies, University of Technology, Sydney.

[9] The University of Queensland Diamantina Institute, The University of Queensland, Woolloongabba, QLD 4102, Australia.

Abstract

Background: The poor bone health of men with prostate cancer on ADT is well-documented but this is not the case for other patient groups with prostatic diseases. The present study aims at investigating the bone health of men on the prostate cancer continuum; hence presented here is the secondary analysis of the Dubbo Osteoporosis Epidemiology Study, focussing on men with diseased prostates. **Methods**: We identified 484 prostate cancer-free controls, and 53 men with BPH and 53 men with prostate cancer (27 on ADT and 26 hormone-naïve) who were diagnosed after enrolment in this study. We conducted logistic regression analysis to determine the association between prostatic disease and the incidence of post-diagnostic osteoporosis. Cox proportional regression was also used to determine the impact of prostatic disease on post-diagnosis fracture risk. **Results**: The incidence of osteoporosis after diagnosis of prostatic disease was 20.8% in men with BPH, 23.1% in hormone-naïve men with prostate cancer, and 44.4% in men with prostate cancer on ADT. The odds ratio for incident osteoporosis/osteopenia at the lumbar spine was 0.32 (95% CI: 0.11-0.92; p=0.04) for men with BPH when compared with men

with prostate cancer on ADT. Post-diagnostic fractures were present in 18.4% of men with BPH, 36.3% of hormone-naïve men with prostate cancer, and 48.0% of men with prostate cancer on ADT. **Conclusion**: This paper thus reveals that poor bone health is a significant problem in men with diseased prostates, and not just men on ADT. It is therefore important to implement bone health management strategies and preventative behaviours even before treatment with ADT.

Keywords
Osteoporosis, prostatic neoplasm, benign prostatic hyperplasia, osteoporosis, bone fractures

Introduction

Benign prostatic hyperplasia (BPH) and prostate cancer are highly prevalent in elderly men (1,2). There are many treatment modalities for prostate cancer including active surveillance, radiation therapy and androgen deprivation therapy (ADT), all of which impact on the physical and psychological wellbeing of these patients. Severe hypogonadism, as a result of treatment with ADT, and its related side-effects have been extensively researched (3-5). A well-accepted adverse effect of ADT is severe bone loss that leads to osteoporosis, which affects 9-53% of men with prostate cancer on ADT (6). On the other hand, only 4-38% of hormone-naïve men with prostate cancer have osteoporosis (7), which could be age-related and/or secondary to treatment such as radiation therapy. There is evidence to suggest that external beam radiation therapy leads to hypogonadism (8,9), which may impact the bone health of hormone-naïve men with prostate cancer in similar fashion to their ADT counterparts. Osteoporosis has devastating outcomes that increases morbidity and mortality (10).

Osteoporosis and low bone mass (osteopenia) increase the risks of fragility fractures (11). In men with prostate cancer fractures are a result of osteoporosis, which is secondary to ADT (12), or fractures are pathological, which is secondary to metastases (13). In those treated with ADT, fractures have been associated with a decrease in overall survival (13). A large proportion of the literature on male bone health focusses on ADT in prostate cancer. There are some studies investigating the bone health of hormone-naïve men with prostate cancer and even fewer studies investigating men with BPH. Since prostatic diseases (prostate cancer and BPH) are age-related diseases, it is important to expand the research focus beyond ADT. Therefore this paper aims to investigate the bone health

of men on a prostatic disease continuum, including two hormonally diverse groups. The secondary aims of the study are to identify the effect of the diagnosis of a prostatic disease on the incidence of osteoporosis and/or osteopenia; and the incidence of fractures. Men with BPH and hormone-naïve men with prostate cancer are hypothesized to have a lower incidence of osteoporosis and fractures than men with prostate on ADT.

Materials and methods

The present secondary analysis is based on the data collected in the Dubbo Osteoporosis Epidemiology Study (DOES), which was initiated in 1989 and is an ongoing prospective longitudinal population-based epidemiological investigation. The main objective of DOES was to evaluate the clinical risk factors for fractures among an elderly Australian sub-population (14,15). In brief, all elderly men and women from the city of Dubbo were invited to participate in this study, with follow-up conducted every two years. The study details have been reported previously (14,15). Data collected between 1989 and 2012, at two year intervals between each visit, have been used here. The St Vincent's Campus Research Ethics Committee approved this study, and written informed consent was obtained for all study participants.

By the end of 2012, 1479 men had been recruited in DOES. Men reporting a diagnosis of prostate cancer or BPH were classified as cases. The cases were further grouped based on reports of treatment with ADT. Controls were remaining prostate cancer-free males. Men with data collected at one time point only were excluded from this analysis. Only incident cases of prostate cancer and BPH were included in this study while men with prevalent disease were excluded as pre-diagnostic changes in bone health could not be ascertained. Participants in this study have therefore been divided into 4 groups: men with prostate cancer on ADT, hormone-naïve men with prostate cancer, men with BPH and prostate cancer-free controls (see Figure 2.1). Pre-diagnostic data were defined as data collected at enrolment of DOES (baseline) while post-diagnostic data were defined as data collected closest to year of prostatic diseases diagnosis.

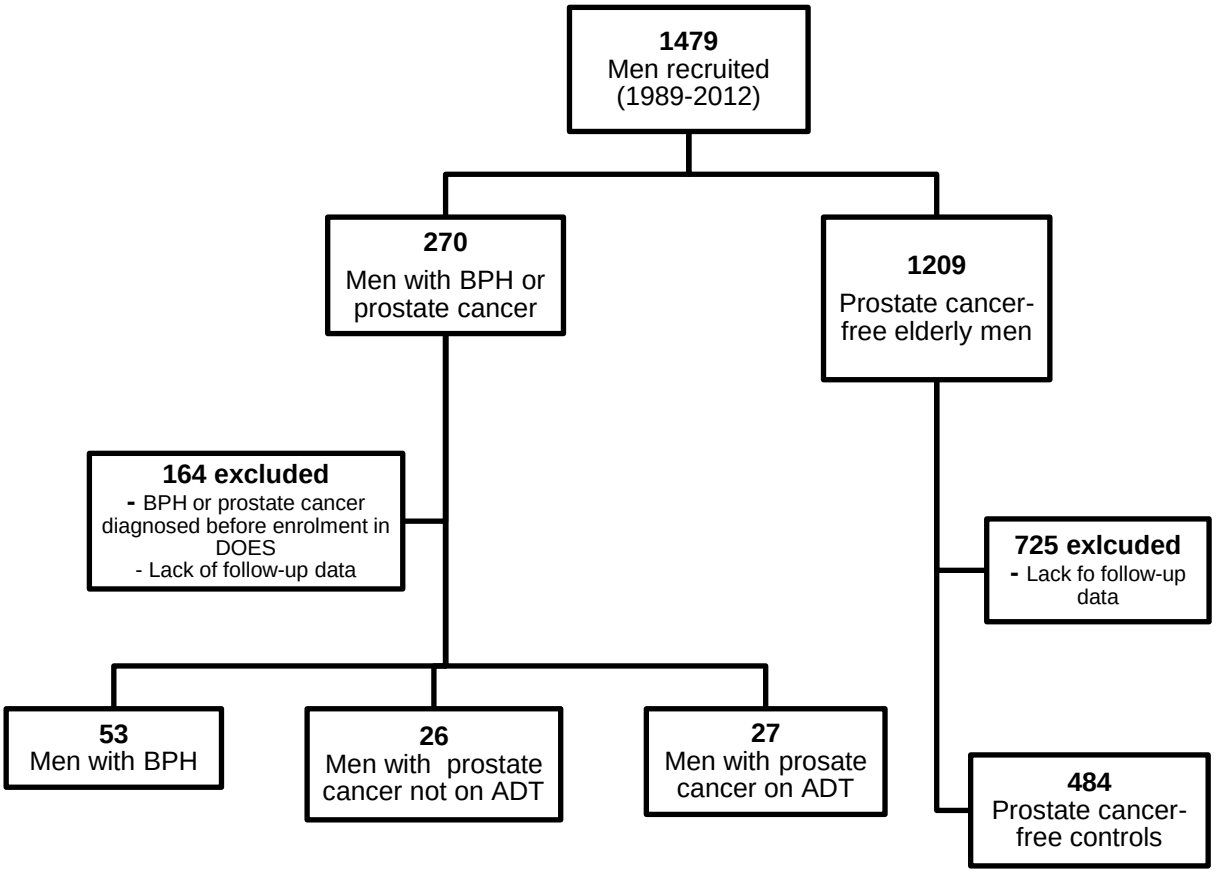


Figure 2.1 Flowchart representing participants included and excluded from the secondary analysis of Dubbo Osteoporosis Epidemiology Study on the bone health of men with BPH or prostate cancer.

BPH, benign prostatic hyperplasia; ADT, androgen deprivation therapy; DOES, Dubbo Osteoporosis Epidemiology Study.

Baseline and follow-up data (at year of prostatic disease diagnosis), including age, medical history, medication and supplement use, and smoking status, were collected by the nurse coordinator during a structured interview. Weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) were measured in light clothing and without shoes using an electronic scale and wall-mounted stadiometer, respectively. Calcium intake was determined using a calcium-specific food frequency questionnaire (98) and smoking was defined as past or

present tobacco intake. Dietary calcium was measured at baseline and every five years, with the latter not coinciding with prostatic disease diagnosis time point for many participants. Only dietary calcium intake at baseline was included here, since it was the most complete dietary variable available for all participants.

Dual energy x-ray absorptiometry (Lunar DPX and Prodigy densitometers; Lunar Radiation Corporation, Madison, Wisconsin, USA) was used to measure bone mineral density (BMD in g/cm^2) at lumbar spine (LS), femoral neck (FN), Ward's triangle and trochanter. BMD was measured at baseline and at multiple times during the follow-up period at approximately 2-year intervals. In all cases the right hip was scanned unless a hip fracture or hip replacement had occurred in which case the left hip was scanned. Because of differences between BMD measured on the two DXA scanners (16), BMD was stratified based on the WHO osteoporosis diagnostic criteria (17), where a T-score ≤ -2.5 was classified as osteoporosis, -2.5 < T-score ≤ -1 was classified as low bone mass (osteopenia), and T-score > -1 was classified as normal bone mass. In multivariate analyses osteoporosis and osteopenia were grouped together as the number of osteopenic cases was too small. The number of non-trauma fractures for all participants was recorded. For cases only, the prevalence of non-trauma fractures before and after diagnosis was calculated.

Statistical analyses

To determine the difference between participants' characteristics at enrolment of DOES, continuous variables were compared using one-way between-groups ANOVA with Post Hoc comparisons using Tukey HSD test. For non-normally distributed continuous variables the Kruskal-Wallis test was used. For categorical variables, Chi-square test was used. Significant difference was determined at $p < 0.05$. The same univariate tests were applied on outcome variables collected at time of prostate cancer or BPH diagnosis.

To determine whether the diagnosis of prostate cancer (ADT or not on ADT) or BPH affected the incidence osteoporosis/osteopenia, a logistic regression model for each skeletal site (LS and FN) was conducted. Dietary calcium, age, BMI, and years since diagnosis were associated with incidence of osteoporosis/osteopenia in univariate models, hence were included in the logistic regression models. For the LS model, the predictors forced in the models were age, BMI, prostate health, and years since diagnosis. For the

FN model, the predictors forced in the model were age, BMI, prostate health, number of years since diagnosis, and calcium intake at baseline for the FN.

Cox proportional hazards regression analysis was used to determine the risk of fractures occurring between time diagnosis of a prostatic disease and last follow up visit recorded, while adjusting for number of fractures before diagnosis and incidence of osteoporosis at the LS and FN. The computer software used for all statistical analyses was Statistical Package for the Social Sciences (SPSS; version 22, IBM Corporation). Participants with missing data on prostate health and BMD were excluded from all analyses.

Results

Characteristics at baseline

The DOES dataset comprised 1479 men (1989 - 2012), of which 270 were diagnosed with BPH or prostate cancer. Over half (n = 164) were excluded as they were either diagnosed with a prostatic disease before enrolment in the study or because they did not complete the first follow-up visit. A total of 53 men with BPH, 27 men with prostate cancer on ADT and 26 hormone-naïve men with prostate cancer were included in this study (see Figure 2.1). Controls who were lost at follow-up were also excluded leaving a total number of 484. The characteristics of study participants at baseline are presented in Table 2.1. Age was significantly different between the groups with hormone-naïve men with prostate cancer being younger than controls (p = 0.004). The median time from enrolment (baseline measurement) and year of prostatic disease diagnosis was 6 years (range 0 - 21).

Characteristics at year of prostatic disease diagnosis

The incidence of LS osteoporosis/osteopenia was 20.8% (n = 11) in men with BPH, 23.1% (n = 6) in hormone-naïve men with prostate cancer, and 44.4% (n = 12) in men with prostate cancer on ADT (p = 0.068). At the FN, the incidence of osteoporosis was 59.2% (n = 29) in men with BPH, 50.0% (n = 12) in hormone-naïve men with prostate cancer, and 51.9% (n = 14) in men with prostate cancer on ADT (p = 0.706). Multinomial logistic regression was performed to assess the impact of the respective prostatic diseases, calcium intake at baseline, age, BMI, and/or time since diagnosis on the incidence of osteoporosis/osteopenia at the FN and LS (Table 2.2 and Table 2.3). The odds of having LS osteoporosis/osteopenia are 3.2 times lower in men with BPH than men with prostate cancer on ADT (p = 0.035). Increasing calcium intake slightly reduces the odds (OR = 0.998, p = 0.013) of having osteoporosis/osteopenia at the FN.

Table 2.1 Characteristics of study participants at enrolment in this study

	Prostate cancer no ADT	Prostate cancer ADT	BPH	Controls	*p-value*
Total (n)	26	27	53	484	
Age (yrs)[1]	64.5 (3)[a]	68 (7)	67 (5.5)	68 (7)	0.004
Weight (g)	86.2 (12.2)	79.5 (11.7)	81.2 (12.3)	81.1 (13.1)	0.22
Height (cm)	175.3 (6.3)	174.8 (6.0)	174.5 (5.9)	173.4 (6.7)	0.23
BMI (kg/cm^2)	28.1 (4.1)	26.1 (3.9)	28.7 (4.0)	29.9 (3.8)	0.25
Dietary Calcium Intake (mg)	720 (300)	675 (590)	650 (260)	680 (565)	0.96
Alcohol intake (g)[1]	40 (43)	15 (133)	10 (40)	12 (46)	0.10
LS BMD (g/cm^2)	1.29 (0.20)	1.21 (0.26)	1.29 (0.25)	1.27 (0.20)	0.36
FN BMD (g/cm^2)	0.98 (0.11)	0.95 (0.15)	0.93 (0.13)	0.93 (0.14)	0.42
WT BMD (g/cm^2)	0.81 (0.13)	0.75 (0.17)	0.74 (0.15)	0.75 (0.15)	0.22
TR BMD (g/cm^2)	0.96 (0.14)	0.93 (0.16)	0.92 (0.12)	0.92 (0.15)	0.44
LS Z-score	0.55(1.54)	0.28 (2.20)	0.92 (2.20)	0.68 (1.60)	0.47
LS T-score	0.38 (1.65)	-0.22 (2.21)	0.48 (1.67)	0.21 (1.18)	0.41
FN Z-score	0.12 (0.75)	0.22 (0.99)	0.01 (1.01)	0.13 (1.02)	0.84
FN T-score	-0.81 (0.87)	-0.93 (1.09)	-1.13 (1.06)	-1.05 (1.11)	0.67
Osteoporosis/ Osteopenia at LS, % (n)	25.0 (6)	50.0 (13)	24.5 (13)	22.6 (100)	0.02
Osteoporosis/ Osteopenia at FN, % (n)	34.8 (8)	46.2 (12)	52.8 (28)	56.2 (246)	0.18
Fracture prevalence pre-diagnosis, % (n)	9.1 (2)	8.0 (2)	10.2 (5)		0.95
DXA Machine					
Prodigy, % (n)	26.9 (7)	7.4 (2)	9.4 (5)	14.5 (70)	0.14
Lunar, % (n)	73.1 (19)	92.6 (25)	90.6 (48)	85.5 (414)	
Bisphosphonates, % (n)	0 (0)	0 (0)	5.7 (3)	3.3 (16)	0.43
Calcium Supps, % (n)	3.8 (1)	0 (0)	5.7 (3)	3.7 (18)	0.66
Current Steroid use, % (n)	0 (0)	0 (0)	3.8 (2)	0.6 (3)	0.10
Beta Blocker, % (n)					
Current Smoker, % (n)	4.2 (1)	4.5 (1)	2.3 (1)	4.6 (19)	0.90
Past Smoker, % (n)	75.0 (18)	57.9 (11)	54.8 (23)	60.2 (189)	0.43

BPH, benign prostatic hyperplasia; LS BMD, Lumbar spine bone mineral density; FN BMD, femoral neck bone mineral density ; WT BMD, Ward's triangle bone mineral density; TR BMD, trochanter bone mineral density; DXA, dual x-ray absorptiometry

Mean (SD) presented for continuous variables and [1]median (inter-quartile range) for non-normally distributed variables

Percentage (n) for categorical variables

[a]Kruskal-Wallis test for comparison between with prostate cancer no ADT and controls, p=0.004

Table 2.2 Multivariable relationships between incidence of osteoporosis (at lumbar spine) and the diagnosis of prostatic diseases

		Number of men	Incidence osteoporosis, % (n)	Crude OR[a]	Adjusted[b] OR[a]	95% CI[c]	Sig.[d]
Prostatic disease group	Prostate cancer ADT	27	7.4	1.00	1.00	Referent	
	Prostate cancer no ADT	25	0	0.38	0.54	0.15-1.98	0.35
	BPH	53	1.9	0.33	0.32	0.11-0.92	0.04
Age at diagnosis, years				1.02	1.00	0.92-1.08	0.93
BMI, kg/m^2				0.84	0.84	0.73-0.96	0.01
Years since prostatic disease diagnosis, years				1.24	1.21	0.82-1.79	0.34

a Odds ratio of fracture incidence
b Odds ratio adjusted for all other variables in the table
c Confidence interval for estimate of adjusted odds ratio
d Statistical significance of the adjusted odds ratio

Post-diagnostic fractures

The numbers of years between diagnosis and incidence of first fracture varied between zero and 17 years (mean 1.8 years, SD = 3.6 years). Post-diagnostic fractures occurred in 18.4% of men with BPH, 36.3% of hormone-naïve men with prostate cancer, and 48% of men with prostate cancer on ADT. The hazard of post-diagnostic fractures was lower in men with BPH when compared with men with prostate cancer on ADT (HR: 0.284, 95% CI = 0.091 - 0.892; p = 0.031) when adjusting for number of fractures pre-diagnosis and incidence of osteoporosis (at LS and FN) at baseline. This difference in hazard was no longer seen when adjusting for incidence of osteoporosis (at LS and FN) at diagnosis.

Table 2.3 Multivariable relationships between incidence of osteoporosis (at femoral neck) and the diagnosis of prostatic diseases

		Number of men	Incidence osteoporosis, % (n)	Crude OR[a]	Adjusted[b] OR[a]	95% CI[c]	Sig.[d]
Prostatic disease group	Prostate cancer ADT	27	4.2	1.00	1.00	Referent	
	Prostate cancer no ADT	23	7.4	0.93	1.56	0.422-5.781	0.504
	BPH	48	12.2	1.35	1.77	0.60-5.23	0.301
Age at diagnosis, years				1.02	1.00	0.93-1.08	0.937
BMI, kg/m^2				0.87	0.90	0.79-1.01	0.076
Years since prostatic disease diagnosis, years				0.76	0.72	0.46-1.13	0.154
Ca intake at baseline, mg				0.998	0.998	0.996-1.00	0.013

a Odds ratio of fracture incidence
b Odds ratio adjusted for all other variables in the table
c Confidence interval for estimate of adjusted odds ratio
dStatistical significance of the adjusted odds ratio

Discussion

The prevalence of osteoporosis is comparable in men with prostate cancer on ADT and not on ADT at time of diagnosis, suggesting that any differences in the progression of this bone disease can be due to treatment side-effects. For example, the lack of difference between men on ADT and the hormone-naïve group was likely due to recent treatment with ADT, less than one year, whereby bone loss had not lead to osteoporosis yet. This is in line with previous studies reporting on the deleterious effects of ADT on BMD over time (18,19). There is also evidence supporting the negative impact of localized treatments on bone health of men with prostate cancer, notably radiation therapy (8,9). The mechanism underlying this effect is the testicular damage secondary to radiation, resulting in low testosterone levels for up to 8 years (9). Such low levels in testosterone may be responsible for some degree of bone loss but not to the same extent as ADT. In other words men with prostate cancer have poor bone health that is likely to worsen upon treatment.

Men with BPH were less likely to have osteoporosis at the LS than men with prostate cancer on ADT at time of diagnosis. As mentioned previously, this is not likely to be due to pharmacological management as these would have been prescribed for long enough to exert such effects. This finding, more specifically the potential mechanism for such effect is unclear. Further investigations into the various circulating growth factors and BMD will help identify pathophysiological candidates associated with this protective/adverse effect.

The difference in post-diagnostic fractures was expected between men with BPH and men with prostate cancer on ADT, as the latter treatment leads to porous bone that is more prone to fragility fractures (18,20). Metastases are also responsible for pathological fractures in men with prostate cancer, whether on ADT or not (21); therefore it explains the difference between men with BPH and men with prostate cancer on ADT, who might have metastatic disease. The lack of difference between hormone-naïve prostate cancer and their ADT counterparts was surprising. This could be a result of our inability to control for certain confounders that were not collected as part of this study. The confounders that impact on fracture risk in men with prostate cancer include presence of metastases, time since ADT initiation, disease stage and grade, and radiation therapy (12).

A strength of this study was the comparison of the bone health of men with BPH with the bone health of men with prostate cancer (on ADT and not). This is a novel approach as most studies to date have compared healthy men to those with prostate cancer (6, 7). The current analysis has greater clinical implications, as it supports bone health monitoring of patients presenting with BPH rather than only focussing on the cancer patients on ADT. While bone health monitoring of the latter group is critical, a preventative approach may be more effective in men with BPH.

Because of inherent challenges in longitudinal studies, we could not evaluate the longitudinal effects of prostatic diseases on the progression of poor bone health. For example, longitudinal statistical modelling could not be applied here due to the inconsistencies in the number of follow-up visits across the study participants. Exclusions of study participants to meet such criteria would lead to small number of cases (prostate cancer and BPH) that would compromise statistical power. Post-hoc sample size calculations revealed that a minimum of 202 hormone-naïve men with prostate cancer and those on ADT would have been needed to conclude that the current incidences of osteoporosis (at LS) were statistically different. This study reports on poor bone health in

men with diseased prostates and adds to the growing body of evidence that osteoporosis is a disease that affects men as well as women.

Conclusions

This paper thus reveals that poor bone health is a significant problem in men with diseased prostates, and not just men on ADT. It is therefore important to implement bone health management strategies and preventative behaviours even before treatment with ADT. The current prostate cancer guidelines (22) recommend bone health management strategies upon ADT initiation but there is evidence that it has not been translated to practice (23,24). It is possible that early lifestyle changes on the prostate cancer continuum (or even BPH) might reduce the bone-related burden of future ADT treatment. There are also benefits beyond prostate cancer treatments, as prostate cancer survivors can live many years post-treatment.

Funding

The Dubbo Osteoporosis Epidemiology Study was supported in part by the National Health and Medical Research Council (NHMRC) grant 276413. This study also received support from the MBF Living Well Foundation; the Ernst Heine Foundation; and untied grants from Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Servier, and Novartis.

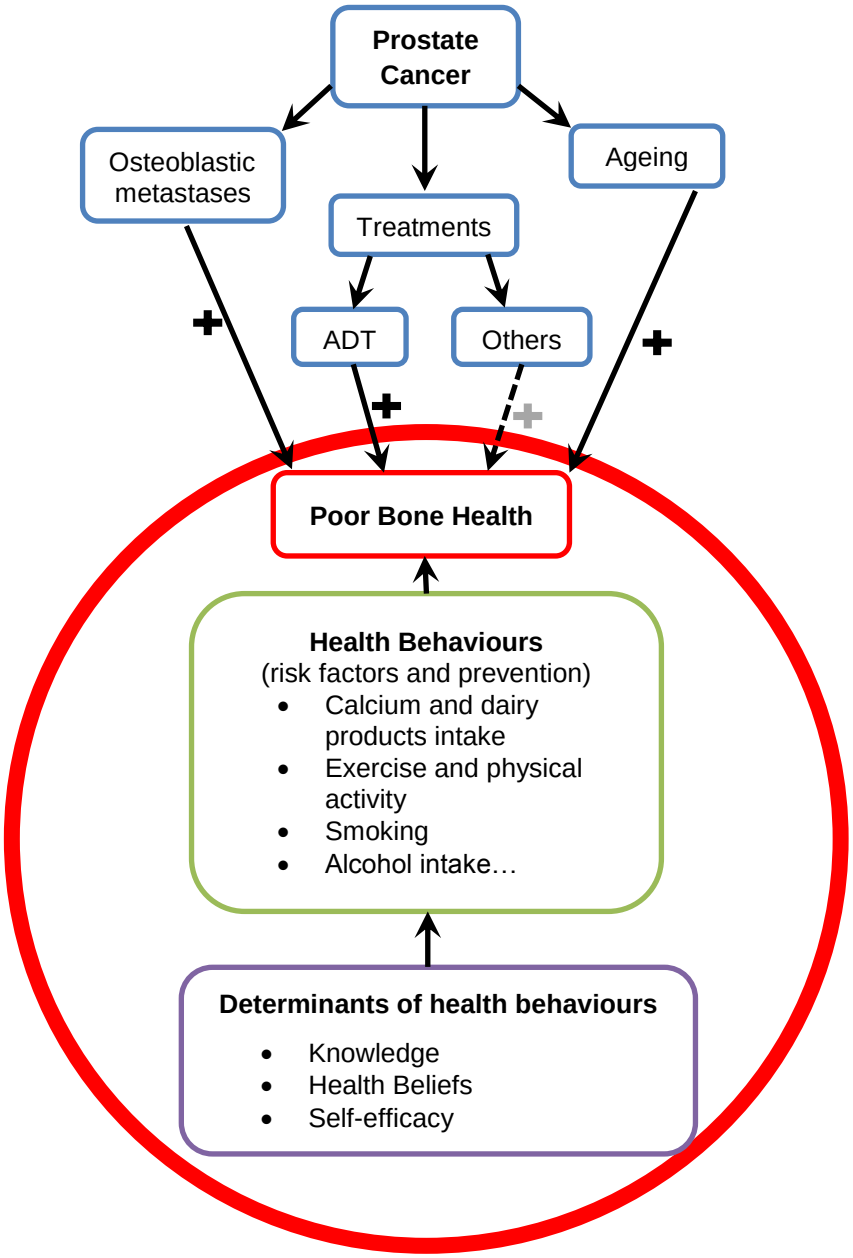
References

1. Wei JT, Calhoun E, Jacobsen SJ. UROLOGIC DISEASES IN AMERICA PROJECT: BENIGN PROSTATIC HYPERPLASIA. The Journal of Urology 2005;173(4):1256-1261.
2. Ferlay J., Shin H.R., Bray F., Forman D., Mathers D., Parkin D.M. Cancer Incidence and Mortality Worldwide: IARC CancerBase No10. GLOBOCAN 2008 v12. Volume 2011. Lyon, France: International Agency for Research on Cancer; 2010.
3. Alibhai SMH, Gogov S, Allibhai Z. Long-term side effects of androgen deprivation therapy in men with non-metastatic prostate cancer: A systematic literature review. Crit Rev Oncol Hematol 2006;60(3):201-215.
4. Haseen F, Murray LJ, Cardwell CR, O'Sullivan JM, Cantwell MM. The effect of androgen deprivation therapy on body composition in men with prostate cancer: systematic review and meta-analysis. J Cancer Surviv 2010;4(2):128-139.
5. Niraula S, Le LW, Tannock IF. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: A systematic review of randomized trials. J Clin Oncol 2013;31(16):2029-2036.

6. Lassemillante A-CM, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors: A meta-analysis. Endocrine 2014;45(3):370-381.
7. Lassemillante A-CM, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors II: A meta-analysis of men not on androgen deprivation therapy. Endocrine 2015.
8. Pickles TOM, Graham P. What Happens to Testosterone After Prostate Radiation Monotherapy And Does it Matter? The Journal of Urology 2002;167(6):2448-2452.
9. Daniell HW, Clark JC, Pereira SE, Niazi ZA, Ferguson DW, Dunn SR, Figueroa ML, Stratte PT. Hypogonadism following prostate-bed radiation therapy for prostate carcinoma. Cancer 2001;91(10):1889-1895.
10. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. The Lancet 1999;353(9156):878-882.
11. Kanis JA, Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report. Osteoporos Int 1994;4(6):368-381.
12. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352(2):154-164.
13. Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal Fractures Negatively Correlate With Overall Survival in Men With Prostate Cancer. The Journal of Urology 2002;168(3):1005-1007.
14. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: The Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporos Int 1994;4(5):277-282.
15. Nguyen T, Sambrook P, Kelly P, Jones G, Lord S, Freund J, Eisman J. Prediction of osteoporotic fractures by postural instability and bone density. Br Med J 1993;307(6912):1111-1115.
16. Frost SA, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Discordance of longitudinal changes in bone density between densitometers. Bone 2007;41(4):690-697.
17. Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994;9(8):1137-1141.
18. Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnick NM. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J Clin Endocrinol Metab 2005;90(12):6410-6417.

19. Mittan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JM. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J Clin Endocrinol Metab 2002;87(8):3656-3661.
20. Higano CS. Androgen-deprivation-therapy-induced fractures in men with nonmetastatic prostate cancer: what do we really know? Nature clinical practice urology 2008;5(1):24-34.
21. Gartrell BA, Saad F. Managing bone metastases and reducing skeletal related events in prostate cancer. Nat Rev Clin Oncol 2014;11(6):335-345.
22. National comprehensive cancer network. NCCN guidelines for prostate cancer (version 2.2014). Volume 2014; 2014.
23. Alibhai SM, Rahman S, Warde PR, Jewett MA, Jaffer T, Cheung AM. Prevention and management of osteoporosis in men receiving androgen deprivation therapy: A survey of urologists and radiation oncologists. Urology 2006;68(1):126-131.
24. Pradhan MR, Mandhani A, Chipde SS, Srivastava A, Singh M, Kapoor R. Bone densitometric assessment and management of fracture risk in Indian men of prostate cancer on androgen deprivation therapy: Does practice pattern match the guidelines? Indian J Urol 2012;28(4):399-404.

CHAPTER 3 BONE HEALTHY BEHAVIOURS AND PSYCHO-BEHAVIOURAL AND PSYCHO-SOCIAL FACTORS



The previous chapters have demonstrated the extent of the osteoporosis problem among men with prostate cancer, regardless of hormonal status. While poor bone health is a well-known side-effect of ADT, less is known about preventative strategies and drivers of such strategies that are specific to men with prostate cancer. Deficits in osteoporosis knowledge have been identified in this population and are likely to result in poor uptake of osteoporosis preventative health behaviours. To confirm this the following studies were performed.

The drivers of healthy bone behaviours are well-research post-menopausal women (99-102), while elderly men at risk of osteoporosis are often ignored (103). Men with prostate cancer are at increased of poor bone health as demonstrated in the previous sections; therefore it is important to understand their health behaviours specific to osteoporosis. This will help inform future interventions, side-effects management strategies, and bone health education programs. There has been recent interest in understanding the drivers of health behaviours in men with prostate cancer (78). A pilot cross-sectional study was conducted to build on such evidence and further explore dietary health behaviours, which may impact on the bone health of men with prostate cancer. Men with prostate cancer and survivors previously participating in a student-led exercise clinic were recruited in this study. A total of 54 men were invited, with 41 consenting and eligible men participating.

The results are presented in the form of two manuscripts, which are currently under review in *American Journal of Men's Health* and *Nutrition and Dietetics*. Section 3.1 focusses on the specific drivers of health behaviours including osteoporosis knowledge, osteoporosis-related health beliefs, and osteoporosis-related self-efficacy. The relationship between these drivers, dietary intake, and bone health status has also been explored. This is followed by section 3.2, which addresses the dietary behaviours of men with prostate cancer and survivors.

3.1 Osteoporosis-related health behaviours in men with prostate cancer and survivors: Exploring osteoporosis knowledge, health beliefs and self-efficacy.

This manuscript describes the psycho-behavioural and psycho-social factors that drive osteoporosis preventative health behaviours in men with prostate cancer and survivors and has been submitted to the *American Journal of Men's Health*.

Date submitted: 9th June 2015

Please note that the reference style for this manuscript is that appropriate for the journal.

Osteoporosis-related health behaviors in men with prostate cancer and survivors: Exploring osteoporosis knowledge, health beliefs and self-efficacy.

Annie-Claude M. Lassemillante[1,2], Tina L. Skinner[3], John D. Hooper[2], John B. Prins[2,4], Olivia R. L. Wright[1,2]

[1] Centre for Dietetics Research (C-DIET-R), School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, QLD 4072, Australia.
[2] Mater Research Institute – University of Queensland, Kent Street, Woolloongabba, QLD 4102, Australia.
[3] Centre for Research on Exercise, Physical Activity and Health (CRExPAH), School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, QLD 4072, Australia.
[4] The University of Queensland Diamantina Institute, The University of Queensland, Woolloongabba, QLD 4102, Australia.

Keywords
Prostatic neoplasm; Survivors; Osteoporosis; Knowledge; Self-efficacy; Health Behaviour

Abstract
Purpose: This descriptive study aimed to (i) determine the extent of osteoporosis knowledge, perceived health beliefs, and self-efficacy with bone healthy behaviors in men with prostate cancer and survivors, and (ii) identify how dietary bone healthy behaviors are associated with these psycho-behavioural and -social factors. *Methods*: Three different questionnaires were used to measure osteoporosis knowledge, health beliefs, and self-efficacy in a group of men with prostate cancer and survivors. Bone health was assessed via dual-energy X-ray absorptiometry and calcium intake using a diet-history. *Results*: The prevalence of osteoporosis and low bone mass was high at over 70%. Participants had inadequate osteoporosis knowledge with a mean score of 43.3% (SD 18%) on the Facts on Osteoporosis Quiz .Participants scored low on the subscale measuring barriers to exercise (median = 11; IQR 6.5), indicating minimal barriers to exercise participation, and the subscale measuring the benefits of exercise scored the highest (median = 24; IQR 3.5) compared with the other subscales. Men with prostate cancer and survivors were highly confident in their exercise and calcium self-efficacy (83.0%, IQR 24.0% and 85.7%, IQR 27.0% respectively). Participants did not meet their calcium requirements or consume

enough dairy products for optimum bone health. *Conclusion*: Men with prostate cancer and survivors have poor osteoporosis knowledge, but are confident in their self-efficacy of undertaking bone healthy behaviors. This confidence did not translate to specific dietary behaviors as they did not meet their calcium or dairy intake requirements. Implications for cancer survivors: There is a need for bone health education programs among prostate cancer survivors. These programs should go beyond education and empowerment to provide practical guidance to maximize uptake of bone healthy behaviors.

Introduction

Men with prostate cancer are increasingly being treated with androgen deprivation therapy (ADT) (Grossmann et al., 2011), which has resulted in better survival rates than a decade ago (National Cancer Institute). Androgen deprivation therapy is associated with increased bone loss leading to a high prevalence of osteoporosis, with up to 53% of men with prostate cancer being diagnosed with the disease (A. C. Lassemillante, Doi, Hooper, Prins, & Wright, 2014). Since osteoporosis has traditionally been seen as a “women’s disease”, there has been less emphasis on educating men about this bone condition resulting in men feeling less susceptible to this disease (McLeod & Johnson, 2011).). A meta-analysis (Laliberté, Perreault, Jouini, Shea, & Lalonde, 2011) on osteoporosis interventions in primary care identified six published studies conducted in men and women (Ashe et al., 2004; Majumdar, Beaupre, Harley, & et al., 2007; Majumdar et al., 2004; D. Solomon et al., 2007; D. H. Solomon et al., 2007; Yuksel, Majumdar, Biggs, & Tsuyuki, 2010), five in women only (Bessette et al., 2008; Cranney et al., 2008; Feldstein et al., 2006; Lafata et al., 2007; Pencille et al., 2009), and none in men only. Evidence suggests that bone health monitoring and interventions, such as promotion of bone healthy behaviors, are poorly implemented at initiation of ADT (Pradhan et al., 2012) despite the presence of other osteoporosis risk factors and co-morbidities (Tanvetyanon, 2005). Such behaviors include adequate intake of calcium (Recommended Dietary Intake is 1000 – 1200 mg per day depending on age (National Osteoporosis Foundation, 2014)) and calcium-containing foods, exercise, smoking cessation, and minimising alcohol intake (National Osteoporosis Foundation, 2014). Calcium is essential to bone health and vitamin D is needed for calcium homeostasis in the body (Lips & van Schoor, 2011). Calcium supplementation, alone or in conjunction with vitamin D supplements, is associated with decreased risk of osteoporotic fractures (Tang, Eslick, Nowson, Smith, & Bensoussan, 2007). The exact role of vitamin D in bone physiology is currently under debate (Peterlik, Kállay, & Cross, 2013; Takahashi, Udagawa, & Suda, 2014), but cross-sectional studies

and clinical trials have demonstrated the protective effects of this vitamin on fracture risk (Lips & van Schoor, 2011). Exercise, notably resistance-training and high-impact loading activities, has a positive impact on hip and/or spine bone mineral density (BMD) of middle-aged and older men (Bolam, van Uffelen, & Taaffe, 2013). Because the epidemiological evidence suggests that diet and exercise have a positive role, many osteoporosis intervention/education studies have included various lifestyle modifications in their protocol (Jean M. Gaines & Marx, 2011; Ryan, Schlidt, & Ryan, 2013).). Clinical guidelines for the management of prostate cancer from the National Comprehensive Cancer Network (2015), make comprehensive recommendations for screening, preventing, and managing poor bone health in men with prostate cancer (especially ADT candidates and users). These include fracture risk assessment; bone density monitoring; calcium and vitamin supplementation; exercise regimes; and allied health involvement (National Comprehensive Cancer Network, 2015).

Nadler et al. (2013) have reported have shown that men with prostate cancer on ADT lack basic osteoporosis knowledge and do not engage in bone healthy behaviors such as participating in exercise, or consuming adequate calcium and vitamin D as measured by food frequency questionnaire (Nadler et al., 2013). A framework that has been used to investigate such phenomenon in osteoporosis research is the Health Belief Model (Janz & Becker, 1984). The Health Belief Model encompasses several primary concepts that predict why individuals will take action to prevent, to screen for, or to control illness conditions. Knowledge, health beliefs, and self-efficacy are modifiable, hence are ideal targets when planning interventions and education programs. This framework has been extensively used in osteoporosis descriptive and intervention studies focussing on women (McLeod & Johnson, 2011). Nadler et al. (2013) are one of the few who have used this framework in men with prostate cancer, and have found that men with prostate cancer on ADT lack basic osteoporosis knowledge and do not engage in bone healthy behaviors. This study therefore aims to add to this small body of literature by determining the extent of osteoporosis knowledge, and perceived health beliefs and self-efficacy related to osteoporosis in men with prostate cancer and survivors. Men with prostate cancer undergoing treatment and survivors are included in this study to replicate the heterogeneity of this population as encountered in clinical practice, thus contributing to the clinical relevance of the findings presented here. The secondary aim of this study is to identify whether dietary bone healthy behaviors and biological markers of bone loss are associated with health beliefs, osteoporosis knowledge, and self-efficacy. The dietary

methodology used in the current study is more robust than the one used by Nadler et al. (2013), therefore providing more accurate information about dietary bone healthy behaviors (Kristal, Peters, & Potter, 2005). Based on the osteoporosis literature and lack of bone health education in men with prostate cancer, we hypothesise that this population has inadequate osteoporosis knowledge and poor dietary behaviors.

Methods

Study Participants

This cross-sectional study was conducted at The University of Queensland, Australia, (September 2013 to June 2014) and included men with prostate cancer and prostate cancer survivors, who attended an exercise clinic. Men with prostate cancer, either undergoing active treatment or not; and prostate cancer survivors (regardless of treatment) were included in this study. Eligible participants were: prostate cancer survivors or men with a current prostate cancer diagnosis; aged over 60 years; either currently undergoing active treatment or not treated; not diagnosed with a bone-related disease; free of cardiovascular, musculoskeletal or metabolic disorders that would have prevented safe participation in exercise; and a body mass less than 150kg. The study was approved by the University of Queensland Medical Research Ethics Committee (2013001160). Informed consent was obtained from all individual participants included in the study.

Instruments

The extent of osteoporosis knowledge was measured using the 26-item Facts on Osteoporosis Questionnaire (FOOQ) that has been validated in men (see Appendix IV). It comprises 20 items from the FOOQ (R. L. Ailinger, Harper, & Lasus, 1998), and 6 items from the Men's Osteoporosis Knowledge Quiz (MOKQ) (Jean M Gaines et al., 2011). The psychometric properties of this 26-item tool were determined in an elderly male population (validity r = 0.076 and Crobach's α = 0.9) (Jean M Gaines et al., 2011). This tool was scored based on the percentage of correct answers, with adequate osteoporosis knowledge defined as a total score of 80% or more (Rita L Ailinger, Braun, Lasus, & Whitt, 2005). The Osteoporosis Self-Efficacy Scale (OSES) was used to measure osteoporosis-specific self-efficacy and consists of 21 items in a visual analogue format (possible score range 0 - 100%; see Appendix V). This tool comprises two subscales measuring confidence for initiating and maintaining calcium intake (OSE-Calcium); and initiating and maintaining exercise habits (OSE-Exercise) (Horan, Kim, Gendler, Froman, & Patel, 1998). The internal consistency of each subscales were r = 0.93 (for OSE-Calcium) and r

= 0.94 (OSE-Exercise) (Horan et al., 1998), and the reliability coefficient of the OSES was α = 0.9 (C. A. Sedlak, Doheny, & Estok, 2000). The Osteoporosis Health Belief Scale (OHBS) was designed with the Health Belief Model as a framework and measures perceived seriousness, perceived susceptibility, perceived benefits, and perceived barriers related to healthy bone behaviors (see Appendix VI). This 42-item tool is divided into six subscales measuring the aforementioned constructs (benefits and barriers measured separately for calcium and exercise) and general health motivation. The responses were recorded on a five-point scale, from "strongly disagree" to "strongly agree", that were awarded a numerical score in increasing order (from 1 to 5). The possible range for each subscale was six to 30, with higher scores meaning higher perceived susceptibility, seriousness, benefits from exercise, benefits from calcium, barriers to exercise, barriers to calcium, and health motivation. The reliability of the OHBS has been tested in a wide range of gender and groups, revealing acceptable levels of reliability (Crobach's α = 0.7 - 0.9) (Shanthi Johnson, McLeod, Kennedy, & McLeod, 2008).

Health and anthropometric measures

The outcomes of interest for the present study were collected during a structured interview and included prostate cancer characteristics and treatments, bone health and osteoporosis status, health behaviors such as smoking, and FRAX® score. Participants with a FRAX® 10-year probability risk < 20% for major fractures were classified as needing osteoporosis intervention (Kanis, Johnell, Odén, Johansson, & McCloskey, 2008). Height was measured to the nearest 0.1 cm using a stadiometer and body mass was measured to the nearest 0.1 kg using electronic stand-on scales (A&D Mercury Load Cell Digitizer; A&D Weighting, Melbourne, Australia). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres (kg/m2). Calcium and dairy intake were derived from detailed structured diet histories (using the validated Wollongong diet history form (Martin, 2004) see Appendix VII) collected by an Accredited Practicing Dietitian. Calcium intake was compared with Australian Recommended Dietary Intakes (RDIs) (1000mg for men <70yrs and 1200mg for men >70yrs; (National Health and Medical Research Council, 2005)). Blood tests were taken after an overnight fast in two 10-mL Vacutainers via vein phlebotomy. One Vacutainer was left to clot at room temperature for 20-30 minutes, while the remaining Vacutainer containing anti-coagulants was placed on ice. Both samples were centrifuged at 2,500 rpm for 10 minutes at 4o C, then plasma and serum were separated into aliquots and stored at -80o C until further processing. Samples were thawed on ice and the following biomarkers were tested using the automated Elecsys®

2010/cobas e411 analyser (Roche Diagnostics): serum C-terminal telopeptide of type 1 collagen (CTx; CV of assay 3.0%), plasma osteocalcin (coefficient of variation [CV] of assay 1.5%), plasma procollagen type 1 N propeptide (P1NP; CV of assay 1.5%), plasma free testosterone (CV of assay 2.0%), and plasma total prostate specific antigen (PSA; CV of assay 3.6%). Serum bone-specific alkaline phosphatase (bone ALP) was measured by immunoenzymetric assay (CV assay 4.2%, Immunodiagnostic System [IDS] Ltd.). Plasma vitamin D was measured, with < 50 nmol/L considered as Vitamin D insufficiency, and < 25 nmol/L as Vitamin D deficiency (World Health Organization Group on the Prevention and Management of Osteoporosis, 2003). Body composition and bone mineral density (BMD; at lumbar spine and right femoral neck) were measured using dual-energy X-ray absorptiometry (DXA; Hologic QDR 4500w) and the World Health Organization definition for osteoporosis was used (low bone mass: -1 < T-score > -2.5; osteoporosis: T-score ≤ -2.5) (Kanis & Kanis, 1994).

Statistical analyses

This study was statistically powered for descriptive purposes. All normally distributed outcome variables were reported using means and standard deviations, while non-parametric outcome variables were reported using medians and interquartile range (IQR). Because of the primarily non-parametric nature of the outcome variables, Kendall's Tau (τ) was used to identify correlations between the psycho-behavioural and psycho-social constructs and the health behaviors. Statistical significance was defined as p-value ≤ 0.05. All analyses were completed using the Statistical Package for the Social Sciences (SPSS) software (version 22, IBM).

Results

Disease and participants characteristics

Fifty-four men with prostate cancer and survivors were invited to participate in this study. A total of 41 men with prostate cancer and survivors were included, as 12 declined to participate and one was ineligible to participate. The characteristics of the study participants are presented in Table 3.1. Most of the participants were classified as prostate cancer survivors no longer undergoing active treatment, while 26.8% (n = 11) were currently undergoing ADT. All men reported on their prostate cancer stage (past or present), with 58.5% (n = 24) reporting localized disease, 17% (n = 7) reporting advanced disease, and 24.4% (n = 10) could not recall their disease stage. Radical prostatectomy (48.8%, n = 20) and radiation therapy (34.1%, n = 14) were the most common forms of

interventions reported by the study participants, and the other treatment modalities are presented in Table 3.1. The majority of the men in this study were overweight or obese based on their BMI. Body composition assessment, via DXA, revealed that this sample was obese because the mean fat mass percentage exceeded 30% (30.8 ± 5.1%) (Gallagher et al., 2000). Total PSA was negatively skewed, because two participants had active advanced disease. Testosterone levels varied, as expected, from castrate levels to normal levels (0.03 – 14.4 ng/mL) as this sample comprises a mix of hormone-naïve men and men on ADT.

Table 3.1 Characteristics of men with prostate cancer (n = 41)

Variable	Mean (sd) or Median (IQR)
Age, years[a]	70 (7.5)
Weight, kg	82.6 (10.3)
Height, cm	176.5 (5.6)
BMI, kg/m^2	26.5 (3.2)
BMI classification	
Normal weight (< 25 kg/m^2), % (n)	26.6 (15)
Overweight (25 - 30 kg/m^2), % (n)	46.3 (19)
Obese (> 30 kg/m^2), % (n)	17.1 (7)
Current smoker, % (n)	2.4 (1)
Gleason score (possible range 2-10)[a]	7 (1)
Total PSA, ng/mL[a]	0.04 (0.6)
Time since prostate cancer diagnosis, years[a]	4 (6.5)
Previous or current ADT[b], % (n)	41.5 (17)
Prostate cancer treatment	
Radical prostatectomy, % (n)	48.8 (20)
Radiation therapy, % (n)	34.1 (14)
Brachytherapy, % (n)	2.4 (1)
Radical prostatectomy & Radiation therapy, % (n)	9.8 (4)
Chemotherapy & Radiation therapy, % (n)	2.4 (1)
Body fat percentage	30.8 (5.1)
Lean body mass percentage	66.1 (5.0)
Lumbar spine	
BMD, g/cm$^{2\,a}$	1.1 (0.2)
T-score[a]	-0.1 (2.0)
Z-score[a]	0.8 (2.1)
Right femoral neck	
BMD, g/cm^2	0. 8 (0.1)
T-score	-1.1 (0.6)
Z-score	0.1 (0.7)
Bone health (at any ROI)	
Normal bone mass, % (n)	26.8 (11)
Osteopenia, % (n)	63.4 (26)
Osteoporosis, % (n)	9.8 (4)
Previous fracture, % (n)	61 (25)
FRAX® score for major fractures[a]	4.30 (3.2)
Calcium supplementation, % (n)	19.5 (8)
Calcium intake, mg/day[a,c]	875 (495)
Meeting calcium requirements, % (n)[d]	22 (9)
Vitamin D supplementation, % (n)	26.8 (11)
Plasma vitamin D, nmol/L	101.3 (25.6)
Free Testosterone, ng/mL[a]	3.6 (5.3)
SHBG, nmol/L[a]	47.9 (41.8)
CTx, ng/mL	0.4 (0.2)
Osteocalcin, µg/L	21.6 (8.1)
P1NP, ng/mL[a]	44.5 (29.4)
Bone ALP, µg/L[a]	17.2 (8.0)

Note: IQR, interquartile range; BMI, body mass index; PSA, prostate specific antigen; ADT, androgen deprivation therapy; BMD, bone mineral density; ROI, region of interest; SHBG, sex hormone binding globulin; CTx, C-terminal telopeptide; P1NP, procollagen type 1 N-telopeptide; ALP, alkaline phosphatase. All values for continuous variable are presented as mean (sd), unless otherwise specified.
[a]The values for these variables are presented as median (IQR). [b]Current and past treatment with ADT. cIntake including calcium from supplementation. dBased on calcium intake including calcium supplementation and the age appropriate RDI.

Bone health and related health behaviors

Over 70% of men with prostate cancer and survivors in this study had low bone mass or osteoporosis. According to the FRAX® intervention threshold for major fractures, only 2.5% (n = 1) needed re-assessment of bone health in 5 years and the rest of the sample did not need any intervention. Applying the FRAX® intervention threshold for hip fractures revealed that 2.5% (n = 1) of the sample met the criteria for pharmacological intervention, 7.5% (n = 3) needed re-assessment of bone health in 5 years, and the rest of the sample did not need further interventions. (Kanis, McCloskey, et al., 2008). Bisphosphonates were prescribed to 9.8% (n = 4) of the sample, of which only 1 participant met the FRAX® threshold for osteoporosis intervention. All of the study participants currently taking bisphosphonates were either currently treated with or previously treated with ADT.

Intake of dairy products, such as milk, cheese and yoghurt, ranged from 0 - 840 g per day (median 225 g/day, IQR 210 g/day). While intake of dairy products varied greatly only 2.4% (n = 1) consumed no dairy at all and 9.8 % (n = 4) consumed more than 500 g of dairy products. The rest of the sample consumed between 20 g and 450 g of dairy products per day (56.1% consumed 0 – 250 g dairy products per day and 31.7% consumed 250 – 500 g dairy products per day). Milk was the main type of dairy products consumed (50.7% of dairy intake) followed by yoghurt (23.2% of dairy intake) and cheese (10.4% of dairy intake). Calcium supplementation was reported by 19.5% (n = 8) of men and vitamin D supplementation in 26.8% (n = 11). Calcium intake from dietary sources ranged from 440 mg to 1645 mg per day (median 865 mg/day, IQR 310 mg/day). Total calcium intake, which is the sum of dietary calcium intake and calcium from supplements, ranged from 550 mg to 1970 mg per day (median 875 mg/day, IQR 495 mg/day). Because of these wide ranges of calcium intake and the varying calcium requirements based on different ages, men in this sample were stratified based on whether they met their calcium requirements or not. We found that less than a quarter of men with prostate cancer and survivors (22%) met their calcium requirements, even when taking calcium supplementation into account.

Osteoporosis knowledge, health beliefs and self-efficacy

FOOQ: The majority of men with prostate cancer and survivors had inadequate osteoporosis knowledge, with an average FOOQ score of 43.3% (SD 18%). Most of the participants knew that “osteoporosis affects men and women” as 95.2% (n = 40) answered this question correctly. About three quarters (71.4%, n = 30) of men with prostate cancer and survivors correctly recognised “bone loss increases in men after the age of 70” but

scored poorly (7.2 - 33.3%) on the remaining osteoporosis questions specific to men. For instance only 33.3% were aware of their calcium requirement and 28.6% were aware that low testosterone level (as seen during ADT) is a risk factor for osteoporosis. More worryingly only 7.1% (n = 3) of participants knew that hormone treatment for prostate cancer increases the risks of osteoporosis. Few men (7.1%, n= 3) were aware that body weight affects bone health and 11.9% (n = 5) knew of the elevated risks (notably fractures) associated with osteoporosis.

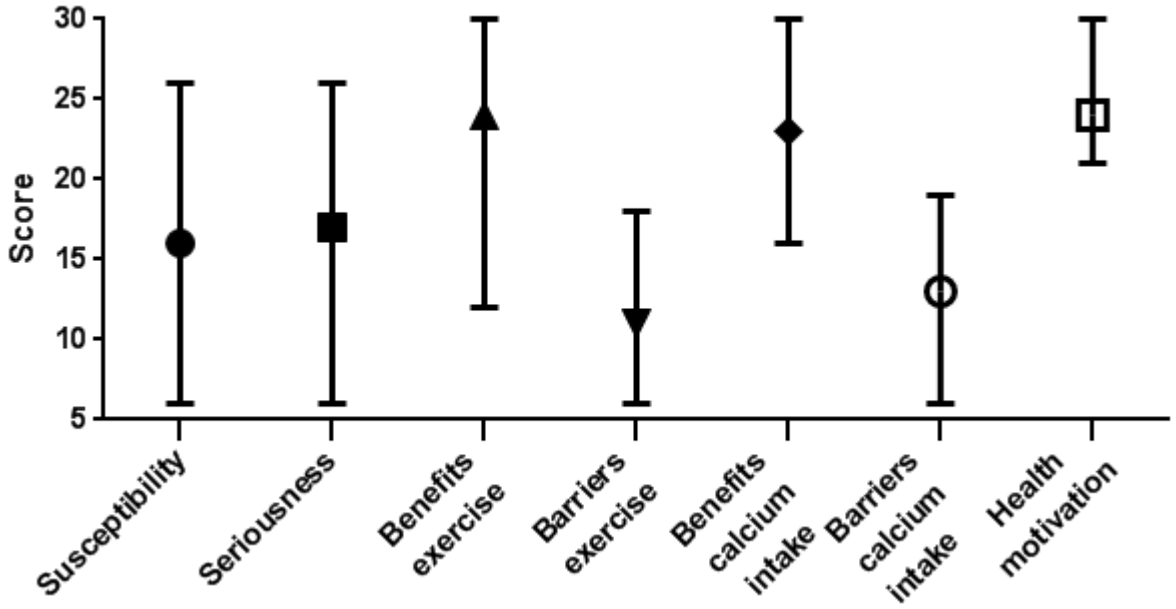


Figure 3.1 Median score on the seven subscales of the Osteoporosis Health Belief Score. Minimum possible score=6 and maximum possible score=30

OHBS and OSES: The OHBS subscale measuring barriers to exercise scored the lowest (median = 11; IQR 6.5), indicating these participants reported minimal barriers to exercise; and the subscale measuring the benefits of exercise scored the highest (median = 24; IQR 3.5) compared with the other subscales. A similar pattern was observed for the perceived barriers and benefits of calcium intake. Participants had a moderate perception of the seriousness of and their susceptibility to osteoporosis (Figure 3.1). Men with prostate cancer and survivors scored highly on the perceived health motivation subscale (median = 24; IQR 5). Men with prostate cancer and survivors showed high confidence on the OSE-Exercise and OSE-Calcium (83.0%, IQR 24.0% and 85.7%, IQR 27.0% respectively). Upon further examination of these subscales, we found that 26.8% (n = 11) and 36.6% (n

= 15) of the study participants were poorly to moderately confident (score < 75% on the visual analogue scale) in their exercise and calcium intake self-efficacy.

Table 3.2 summarizes the correlations between the bone healthy behaviors and the psycho-behavioural and psycho-social factors. The correlations were small to moderate (Cohen, 2003) but similar to previous studies investigating osteoporosis knowledge and health beliefs (Jean M. Gaines & Marx, 2011; McLeod & Johnson, 2011). We found that osteoporosis knowledge was positively correlated with general health motivation ($\tau = 0.26$, $p = 0.05$) and perceived benefits of exercise ($\tau = 0.26$, $p = 0.05$), and negatively correlated with perceived barriers to calcium intake ($\tau = -0.47$, $p < 0.001$). There was a positive correlation between the perceived benefits of exercise and the perceived benefits of calcium intake ($\tau = 0.41$, $p = 0.003$).

Table 3.2 Correlation coefficient (τ) for associations between osteoporosis knowledge, health beliefs and self-efficacy, and osteoporosis behaviors and biomarkers of bone health. Correlation coefficients are highlighted if p ≤ 0.05, with p-values presented in brackets.

n = 33 τ (p-value)	Osteoporosis knowledge	Perceived Susceptibility	Perceived Seriousness	Perceived Benefits Exercise	Perceived Benefits Calcium	Perceived Barriers Exercise	Perceived Barriers Calcium	Health Motivation	Exercise Self-efficacy	Calcium Self-efficacy
Calcium intake	0.03 (0.80)	-0.11 (0.39)	0.21 (0.09)	**0.28** (0.03)	0.14 (0.27)	-0.21 (0.10)	-0.06 (0.62)	0.05 (0.72)	0.13 (0.29)	0.02 (0.90)
Dairy intake	0 (1.00)	0.12 (0.34)	0.11 (0.38)	0.01 (0.91)	0.04 (0.74)	-0.09 (0.50)	0.04 (0.78)	0.13 (0.31)	0.05 (0.71)	-0.04 (0.73)
Number of alcoholic drinks/week	-0.14 (0.27)	0.16 (0.23)	0.09 (0.77)	-0.05 (0.70)	-0.18 (0.18)	0.03 (0.84)	**0.27** (0.04)	0.04 (0.75)	-0.01 (0.96)	-0.04 (0.74)
BMI	-0.13 (0.31)	0.03 (0.79)	0.02 (0.88)	-0.05 (0.69)	0.07 (0.60)	**0.24** (0.06)	**0.26** (0.04)	-0.20 (0.11)	**-0.30** (0.02)	-0.17 (0.16)
FRAX® for major fractures	-0.02 (0.90)	0.17 (0.18)	-0.23 (0.06)	-0.18 (0.16)	**-0.28** (0.03)	-0.12 (0.36)	0.05 (0.67)	-0.06 (0.65)	0.03 (0.83)	0.04 (0.76)
Right Femoral Neck T-score	-0.04 (0.76)	-0.05 (0.68)	**0.34** (0.01)	0.02 (0.86)	0.03 (0.80)	0.10 (0.46)	0.15 (0.23)	.013 (0.31)	-0.21 (0.09)	-0.15 (0.24)
Right Femoral Neck Z-score	-0.11 (0.37)	-0.03 (0.84)	**0.30** (0.02)	-0.08 (0.55)	0.13 (0.34)	0.11 (0.42)	0.17 (0.18)	0.21 (0.11)	-0.17 (0.18)	-0.13 (0.31)
Lumbar Spine T-score	0.07 (0.55)	-0.11 (0.41)	0.23 (0.07)	0.01 (0.96)	0.10 (0.43)	-0.05 (0.68)	-0.18 (0.17)	-0.02 (0.88)	-0.22 (0.07)	0.06 (0.61)
Lumbar Spine T-score	0.06 (0.64)	-0.11 (0.37)	0.18 (0.16)	-0.06 (0.65)	0.05 (0.68)	0.01 (0.96)	-0.11 (0.38)	-0.03 (0.83)	**-0.25** (0.04)	0 (1.00)
CTx (ng/mL)	0.05 (0.70)	0.17 (0.19)	-0.17 (0.17)	**-0.29** (0.02)	-0.14 (0.29)	0.10 (0.44)	-0.04 (0.73)	-0.01 (0.95)	0.04 (0.72)	0.06 (0.61)
OC (ng/mL)	0.08 (0.51)	0.07 (0.61)	-0.15 (0.23)	-0.23 (0.07)	-0.08 (0.56)	0.14 (0.25)	-0.09 (0.49)	0.03 (0.84)	0 (1.00)	0.09 (0.46)
Testosterone (ng/mL)	0 (1.00)	**-0.37** (0.01)	0.22 (0.09)	**0.26** (0.05)	0.21 (0.11)	-0.01 (0.91)	0 (0.98)	-0.03 (0.81)	0.10 (0.42)	-0.07 (0.60)
P1NP (ng/mL)	0.07 (0.56)	0.13 (0.31)	-0.17 (0.18)	**-0.29** (0.03)	-0.12 (0.35)	0.15 (0.24)	-0.06 (0.64)	< 0.00 (0.99)	-0.01 (0.95)	0.10 (0.44)

BMI, body mass index; CTx, C-terminal telopeptide; OC, osteocalcin; P1NP, procollagen type 1 N-telopeptide.

Discussion

Osteoporosis knowledge, health beliefs and prostate cancer

This is the first study to investigate the extent of osteoporosis knowledge, health beliefs, and self-efficacy and their associations with health behaviors in a well-characterised group of prostate cancer survivors. Our sample, although small, was well-characterised in terms of disease profile, bone biomarkers, health behaviors, and behavioural and psycho-social constructs. The significant conclusions for men with prostate cancer and survivors were: (i) over 70% had poor bone health, (ii) they did not consume enough calcium, which is essential to bone health, (iii) the have inadequate osteoporosis knowledge, and (iv) did not perceive they were susceptible to osteoporosis or that it was a serious disease. According to the Health Belief Model (Rosenstock, Strecher, & Becker, 1988) these constructs are important to initiate and maintain health behaviour change. Such change, especially healthy bone behaviors, are important in men with prostate cancer, who have a high prevalence of poor bone health regardless of ADT status (A. C. Lassemillante et al., 2014; A. C. Lassemillante, Doi, Hooper, Prins, & Wright, 2015). Our findings support the idea that osteoporosis is a “silent disease” (Nguyen, Center, & Eisman, 2004) and reflects a lack of osteoporosis education, patient empowerment and bone health monitoring for men with prostate cancer (S. M. Alibhai et al., 2006; Shabbir MH Alibhai, Yun, Cheung, & Paszat, 2012; Tanvetyanon, 2005). On the other hand, the negative statistically significant correlation between testosterone levels and perceived susceptibility to osteoporosis reported here, suggests that hypogonadism may be associated with this health belief. Therefore our results indicate that only those at greatest risk of fractures and osteoporosis are informed of this bone condition, hence neglecting prostate cancer survivors and those not on ADT. Clinical guidelines recommend bone health monitoring and calcium supplementation in prostate cancer patients on ADT (National comprehensive cancer network, 2014), therefore explaining why they may feel more susceptible to poor bone health. Prostate cancer survivors and those not on ADT should not be neglected in terms of bone health education and empowerment as they experience a higher prevalence of osteoporosis and low bone mass than healthy older men (A. C. Lassemillante et al., 2015), likely due to other cancer treatments such as radiation therapy (Daniell et al., 2001). Osteoporosis education focussing on health beliefs alone does not incite behaviour change (Rizzoli, Abraham, & Brandi, 2014), therefore justifying the need for practical information on how to tackle barriers to behaviour change.

Osteoporosis knowledge, health beliefs and dietary behaviors

This study is in line with previous research (A. C. Lassemillante et al., 2015) whereby men with prostate cancer do not meet their calcium requirements despite being at risk of osteoporosis, for example secondary to ADT. We showed this can be in part due to poor osteoporosis knowledge that led to greater barriers to calcium intake. In this study, trends in the results indicated calcium intake was not associated with calcium intake self-efficacy or knowledge, but was more closely linked with perceived exercise benefits. This finding demonstrates the importance of multiple disciplines in osteoporosis education and specific bone healthy behaviors. Despite the positive association between perceived exercise benefits and perceived calcium benefits, this did not equate to adequate calcium intake, highlighting the gap between health beliefs and actual health behaviors. We report here that men with prostate cancer and survivors are not aware of their calcium requirements and this may also help in explaining why they do not meet their requirements. The majority of this sample consumed less than the equivalent of 1 cup of milk per day, which is short of the current recommendations of 2.5 cups per day (National Health and Medical Research Council, 2013). Even those taking calcium supplements fell short of their requirements, likely due to low dietary calcium intake. The positive correlation between confidence in calcium intake self-efficacy and calcium intake suggests that promoting awareness on how to implement healthy bone strategies is more likely to contribute to calcium intake. A recent review of osteoporosis interventions (Ryan et al., 2013) reported that programs that included skills training were more successful at increasing calcium intake than those that did not include such component. Similarly, self-efficacy remained unchanged after many osteoporosis intervention programs (Francis, Matthews, Van Mechelen, Bennell, & Osborne, 2009; Carol A. Sedlak, Doheny, & Jones, 1998; Tung & Lee, 2006) despite improvements in osteoporosis knowledge and health beliefs. Therefore to affect behaviour change we need to go beyond traditional osteoporosis education programs by incorporating other behavioural change theoretical models in the interventions, including social contact, providing longer interventions (over a few months), and be multi-dimensional (Ryan et al., 2013). Rizzoli et al. (2014) discuss such novel approaches that are being implemented in new osteoporosis intervention programs (Gianoudis et al., 2012), but we also believe that dietary interventions need to include individualized care. As a result, the dietary preventative behaviors will be tailored to one's social, family, and financial circumstances. Because men often survive many years after being diagnosed and treated for prostate cancer, it is important to educate them about other aspects of their health, especially those that could have been impacted by cancer

treatments. More osteoporosis intervention studies are needed but these also need to be sex specific. They also need to take into consideration the health behaviors of men with prostate cancer and survivors in providing practical guidance on how to maintain healthy bone behaviors.

Some of the results reported here, such as osteoporosis knowledge, are in accordance with those reported in a cross-sectional study by Nadler et al. (2013); however some results such as calcium adequacy are markedly different. This can be explained by a lower proportion of men taking calcium supplements in the present study (19.5% versus 60% (Nadler et al., 2013)). While both studies present different findings, attributed to differences between the study populations, they both outline the gaps in the bone health (related behaviors and determinants) of men with prostate cancer. A recent intervention by Nadler, Alibhai, Catton, Catton, and Jones (2014), providing written education material on osteoporosis, resulted in increased calcium intake among men with prostate cancer who did not meet their requirements. While this intervention was simple, it was based on established behaviour change models; therefore it suggests that more comprehensive interventions, incorporating allied health professionals and behaviour changed models, may lead to additional health behaviour changes.

Strengths and limitations

Because the study participants were recruited from an exercise clinic, their confidence in exercise self-efficacy and other related exercise health beliefs measured here will differ from the rest of the prostate cancer population. This study reports on men with prostate cancer on ADT as well as under-represented groups in prostate cancer research, i.e., prostate cancer survivors and hormone-naïve men with prostate cancer. Given the association between hypogonadism and perceived susceptibility to osteoporosis, we anticipate that investigating hormone-naïve men with prostate cancer and survivors will result in poorer psycho-behavioural and psycho-social scores than reported here. The tool measuring calcium and exercise self-efficacy specifies what exercise means (“activities such as walking, swimming, golfing, biking, aerobic dancing”) but does not give examples of the terminology “calcium-rich foods”, which is used throughout this questionnaire. As a result the calcium intake self-efficacy responses might be biased for men who may not be aware of examples of calcium-rich foods; unfortunately, such bias could not be controlled for as we did not collect data on their osteoporosis-specific dietary knowledge. Although the sample is small, hence associated statistical analyses problematic, it offers a glimpse

of the gap in osteoporosis education in men with prostate cancer and survivors while raising further questions for research and practice. The present findings are not likely to be unique to men with prostate cancer, but this conclusion cannot be made due to the absence of a control group, such as healthy men. A strength of this study is the robust dietary methodology used to measure calcium intake that is more accurate than the methods used in similar studies (Nadler et al., 2013; Ryan et al., 2013) that have used calcium questionnaires or food frequency questionnaire to gather such data.

Conclusion

We can conclude that men with prostate cancer and survivors have inadequate osteoporosis knowledge, regardless of ADT status. It is concerning as one would expect that men on ADT would have better knowledge of this bone condition and subsequent bone healthy behaviors since it is a side-effect of their treatment. Intervention program designed for men with prostate cancer and survivors are required to address treatment-related bone loss and health behaviors that they may have adopted to manage their cancer. Our findings support the complementary role of the multi-discipline approach to the management of bone health post-prostate cancer treatment. This approach should also be individually tailored, while being innovative to effect sustainable behaviour change.

References

Ailinger, R. L., Braun, M. A., Lasus, H., & Whitt, K. (2005). Factors influencing osteoporosis knowledge: a community study. Journal of Community Health Nursing, 22(3), 135-142.

Ailinger, R. L., Harper, D. C., & Lasus, H. A. (1998). Bone up on osteoporosis. Development of the Facts on Osteoporosis Quiz. Orthopaedic Nursing, 17(5), 66-73.

Alibhai, S. M., Rahman, S., Warde, P. R., Jewett, M. A., Jaffer, T., & Cheung, A. M. (2006). Prevention and management of osteoporosis in men receiving androgen deprivation therapy: A survey of urologists and radiation oncologists. Urology, 68(1), 126-131. doi:10.1016/j.urology.2006.01.054

Alibhai, S. M., Yun, L., Cheung, A. M., & Paszat, L. (2012). Screening for osteoporosis in men receiving androgen deprivation therapy. JAMA: the journal of the American Medical Association, 307(3), 255-256. doi:10.1001/jama.2011.2022.

Ashe, M., Khan, K., Guy, P., Kruse, K., Hughes, K., O'Brien, P., McKay, H. (2004). Wristwatch—distal radial fracture as a marker for osteoporosis investigation:: A controlled

trial of patient education and a physician alerting system. Journal of Hand Therapy, 17(3), 324-328. doi:http://dx.doi.org/10.1197/j.jht.2004.04.001
Bessette, L., Ste-Marie, L.-G., Jean, S., Shawn Davison, K., Beaulieu, M., Baranci, M., Brown, J. P. (2008). Recognizing osteoporosis and its consequences in Quebec (ROCQ): Background, rationale, and methods of an anti-fracture patient health-management programme. Contemporary Clinical Trials, 29(2), 194-210. doi:http://dx.doi.org/10.1016/j.cct.2007.07.007
Bolam, K. A., van Uffelen, J. G. Z., & Taaffe, D. R. (2013). The effect of physical exercise on bone density in middle-aged and older men: A systematic review. Osteoporosis International, 24(11), 2749-2762. doi:10.1007/s00198-013-2346-1
Cohen, J. (2003). Applied multiple regression/correlation analysis for the behavioral sciences. Mahwah, N.J: L. Erlbaum Associates.
Cranney, A., Lam, M., Ruhland, L., Brison, R., Godwin, M., Harrison, M. M., Graham, I. D. (2008). A multifaceted intervention to improve treatment of osteoporosis in postmenopausal women with wrist fractures: a cluster randomized trial. Osteoporosis International, 19(12), 1733-1740. doi:10.1007/s00198-008-0669-0
Daniell, H. W., Clark, J. C., Pereira, S. E., Niazi, Z. A., Ferguson, D. W., Dunn, S. R., Stratte, P. T. (2001). Hypogonadism following prostate-bed radiation therapy for prostate carcinoma. Cancer, 91(10), 1889-1895. doi:10.1002/1097-0142(20010515)91:10<1889::AID-CNCR1211>3.0.CO;2-U
Feldstein, A., Elmer, P. J., Smith, D. H., Herson, M., Orwoll, E., Chen, C., Swain, M. C. (2006). Electronic Medical Record Reminder Improves Osteoporosis Management After a Fracture: A Randomized, Controlled Trial. Journal of the American Geriatrics Society, 54(3), 450-457. doi:10.1111/j.1532-5415.2005.00618.x
Francis, K. L., Matthews, B. L., Van Mechelen, W., Bennell, K. L., & Osborne, R. H. (2009). Effectiveness of a community-based osteoporosis education and self-management course: a wait list controlled trial. Osteoporosis International, 20(9), 1563-1570. doi:10.1007/s00198-009-0834-0
Gaines, J. M., & Marx, K. A. (2011). Older men's knowledge about osteoporosis and educational interventions to increase osteoporosis knowledge in older men: A systematic review. Maturitas, 68(1), 5-12. doi:http://dx.doi.org/10.1016/j.maturitas.2010.08.013
Gaines, J. M., Marx, K. A., Narrett, M., Caudill, J., Landsman, J., & Parrish, J. M. (2011). Validation of the male osteoporosis knowledge quiz. American journal of men's health, 5(1), 78-83.

Gallagher, D., Heymsfield, S. B., Heo, M., Jebb, S. A., Murgatroyd, P. R., & Sakamoto, Y. (2000). Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. The American Journal of Clinical Nutrition, 72(3), 694-701. Retrieved from http://ajcn.nutrition.org/content/72/3/694.abstract

Gianoudis, J., Bailey, C., Sanders, K., Nowson, C., Hill, K., Ebeling, P., & Daly, R. (2012). Osteo-cise: Strong Bones for Life: Protocol for a community-based randomised controlled trial of a multi-modal exercise and osteoporosis education program for older adults at risk of falls and fractures. BMC Musculoskeletal Disorders, 13(1), 78. Retrieved from http://www.biomedcentral.com/1471-2474/13/78

Grossmann, M., Hamilton, E. J., Gilfillan, C., Bolton, D., Joon, D. L., & Zajac, J. D. (2011). Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy. Medical Journal of Australia, 194(6), 301-306.

Horan, M. L., Kim, K. K., Gendler, P., Froman, R. D., & Patel, M. D. (1998). Development and evaluation of the osteoporosis self-efficacy scale. Research in Nursing and Health, 21(5), 395-403.

Janz, N. K., & Becker, M. H. (1984). The Health Belief Model: A decade later. Health Education and Behavior, 11(1), 1-47.

Kanis, J. A., Johnell, O., Odén, A., Johansson, H., & McCloskey, E. (2008). FRAX® and the assessment of fracture probability in men and women from the UK. Osteoporosis International, 19(4), 385-397. doi:10.1007/s00198-007-0543-5

Kanis, J. A., & Kanis, J. A. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report. Osteoporosis International, 4(6), 368-381. doi:10.1007/bf01622200

Kanis, J. A., McCloskey, E. V., Johansson, H., Strom, O., Borgstrom, F., & Oden, A. (2008). Case finding for the management of osteoporosis with FRAX®—assessment and intervention thresholds for the UK. Osteoporosis International, 19(10), 1395-1408. doi:10.1007/s00198-008-0712-1

Kristal, A. R., Peters, U., & Potter, J. D. (2005). Is it time to abandon the food frequency questionnaire? Cancer Epidemiology Biomarkers & Prevention, 14(12), 2826-2828. doi:10.1158/1055-9965.epi-12-ed1

Lafata, J., Kolk, D., Peterson, E., McCarthy, B., Weiss, T., Chen, Y.-T., & Muma, B. (2007). Improving Osteoporosis Screening: Results from a Randomized Cluster Trial. Journal of General Internal Medicine, 22(3), 346-351. doi:10.1007/s11606-006-0060-9

Laliberté, M. C., Perreault, S., Jouini, G., Shea, B. J., & Lalonde, L. (2011). Effectiveness of interventions to improve the detection and treatment of osteoporosis in primary care

settings: a systematic review and meta-analysis. Osteoporosis International, 22(11), 2743-2768. doi:10.1007/s00198-011-1557-6
Lassemillante, A.-C. M., Doi, S. A., Hooper, J. D., Prins, J. B., & Wright, O. R. (2014). Prevalence of osteoporosis in prostate cancer survivors: A meta-analysis. Endocrine, 45(3), 370-381. doi:10.1007/s12020-013-0083-z
Lassemillante, A.-C. M., Doi, S. A., Hooper, J. D., Prins, J. B., & Wright, O. R. (2015). Prevalence of osteoporosis in prostate cancer survivors II: A meta-analysis of men not on androgen deprivation therapy. Endocrine. doi:10.1007/s12020-015-0536-7
Lips, P., & van Schoor, N. M. (2011). The effect of vitamin D on bone and osteoporosis. Best Practice & Research Clinical Endocrinology & Metabolism, 25(4), 585-591. doi:http://dx.doi.org/10.1016/j.beem.2011.05.002
Majumdar, S. R., Beaupre, L. A., Harley, C. H., & et al. (2007). Use of a case manager to improve osteoporosis treatment after hip fracture: Results of a randomized controlled trial. Archives of Internal Medicine, 167(19), 2110-2115. doi:10.1001/archinte.167.19.2110
Majumdar, S. R., Rowe, B. H., Folk, D., Johnson, J. A., Holroyd, B. H., Morrish, D. W., Russell, A. S. (2004). A controlled trial to increase detection and treatment of osteoporosis in older patients with a wrist fracture. Annals of Internal Medicine, 141(5), 366-373.
Martin, G. S. (2004). The interviewer-administered, open-ended diet history method for assessing usual dietary intakes in clinical research: relative and criterion validation studies. (Doctorate of Philosophy), University of Wollongong.
McLeod, K. M., & Johnson, C. S. (2011). A systematic review of osteoporosis health beliefs in adult men and women. Journal of osteoporosis, 2011.
Nadler, M., Alibhai, S., Catton, P., Catton, C., & Jones, J. (2014). The impact of bone mineral density testing, fracture assessment, and osteoporosis education in men treated by androgen deprivation for prostate cancer: A pilot study. Supportive Care in Cancer, 22(9), 2409-2415. doi:10.1007/s00520-014-2183-6
Nadler, M., Alibhai, S., Catton, P., Catton, C., To, M. J., & Jones, J. M. (2013). Osteoporosis knowledge, health beliefs, and healthy bone behaviours in patients on androgen-deprivation therapy (ADT) for prostate cancer. BJU International, n/a-n/a. doi:10.1111/j.1464-410X.2012.11777.x
National Cancer Institute. SEER Cancer Statistics Review 1975-2011: Prostate - Annual Death Rates. Retrieved from http://seer.cancer.gov/csr/1975_2011/browse_csr.php?sectionSEL=23&pageSEL=sect_23_table.06.html

National comprehensive cancer network. (2014, 1st April 2014). NCCN guidelines for prostate cancer (version 2.2014). Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
National Comprehensive Cancer Network (NCCN). (2015, 24 October 2014). NCCN guidelines for prostate cancer (version 1.2015). Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
National Health and Medical Research Council. (2005). Nutrient Reference Values for Australia and New Zealand. Retrieved from
National Health and Medical Research Council. (2013). Australian Dietary Guidelines. Retrieved from Canberra:
Nguyen, T. V., Center, J. R., & Eisman, J. A. (2004). Osteoporosis: Underrated, underdiagnosed and undertreated. Medical Journal of Australia, 180(5), S18.
Pencille, L., Campbell, M., Van Houten, H., Shah, N., Mullan, R., Swiglo, B., Montori, V. (2009). Protocol for the Osteoporosis Choice trial. A pilot randomized trial of a decision aid in primary care practice. Trials, 10(1), 113. Retrieved from http://www.trialsjournal.com/content/10/1/113
Peterlik, M., Kállay, E., & Cross, H. S. (2013). Calcium nutrition and extracellular calcium sensing: Relevance for the pathogenesis of osteoporosis, cancer and cardiovascular diseases. Nutrients, 5(1), 302-327.
Pradhan, M. R., Mandhani, A., Chipde, S. S., Srivastava, A., Singh, M., & Kapoor, R. (2012). Bone densitometric assessment and management of fracture risk in Indian men of prostate cancer on androgen deprivation therapy: Does practice pattern match the guidelines? Indian Journal of Urology, 28(4), 399-404. doi:10.4103/0970-1591.105750
Rizzoli, R., Abraham, C., & Brandi, M.-L. (2014). Nutrition and bone health: turning knowledge and beliefs into healthy behaviour. Current Medical Research and Opinion, 30(1), 131-141. doi:doi:10.1185/03007995.2013.847410
Rosenstock, I. M., Strecher, V. J., & Becker, M. H. (1988). Social Learning Theory and the Health Belief Model. Health Education and Behavior, 15(2), 175-183. doi:10.1177/109019818801500203
Ryan, P., Schlidt, A., & Ryan, C. (2013). The impact of osteoporosis prevention programs on calcium intake: a systematic review. Osteoporosis International, 24(6), 1791-1801. doi:10.1007/s00198-012-2259-4
Sedlak, C. A., Doheny, M. O., & Estok, P. J. (2000). Osteoporosis in older men: knowledge and health beliefs. Orthopaedic Nursing, 19(3), 38-42, 44-36.

Sedlak, C. A., Doheny, M. O., & Jones, S. L. (1998). Osteoporosis Prevention In Young Women. Orthopaedic Nursing, 17(3), 53-60. Retrieved from http://journals.lww.com/orthopaedicnursing/Fulltext/1998/05000/Osteoporosis_Prevention_In_Young_Women_.9.aspx

Shanthi Johnson, C., McLeod, W., Kennedy, L., & McLeod, K. (2008). Osteoporosis Health Beliefs Among Younger and Older Men and Women. Health Education and Behavior, 35(5), 721-733. doi:10.1177/1090198107301331

Solomon, D., Polinski, J., Stedman, M., Truppo, C., Breiner, L., Egan, C., Brookhart, M. A. (2007). Improving Care of Patients At-Risk for Osteoporosis: A Randomized Controlled Trial. Journal of General Internal Medicine, 22(3), 362-367. doi:10.1007/s11606-006-0099-7

Solomon, D. H., Katz, J. N., Finkelstein, J. S., Polinski, J. M., Stedman, M., Brookhart, M. A., Avorn, J. (2007). Osteoporosis Improvement: A Large-Scale Randomized Controlled Trial of Patient and Primary Care Physician Education. Journal of Bone and Mineral Research, 22(11), 1808-1815. doi:10.1359/jbmr.070717

Takahashi, N., Udagawa, N., & Suda, T. (2014). Vitamin D endocrine system and osteoclasts. BoneKEy Rep, 3. doi:10.1038/bonekey.2013.229

Tang, B. M., Eslick, G. D., Nowson, C., Smith, C., & Bensoussan, A. (2007). Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: A meta-analysis. Lancet, 370(9588), 657-666. doi:10.1016/s0140-6736(07)61342-7

Tanvetyanon, T. (2005). Physician practices of bone density testing and drug prescribing to prevent or treat osteoporosis during androgen deprivation therapy. Cancer, 103(2), 237-241. doi:10.1002/cncr.20766

Tung, W. C., & Lee, I. F. K. (2006). Effects of an osteoporosis educational programme for men. Journal of Advanced Nursing, 56(1), 26-34. doi:10.1111/j.1365-2648.2006.03976.x

Waldman, T., Sarbaziha, R., Merz, C. N. B., & Shufelt, C. (2015). Calcium Supplements and Cardiovascular Disease: A Review. American Journal of Lifestyle Medicine, 9(4), 298-307. doi:10.1177/1559827613512593

World Health Organization Group on the Prevention and Management of Osteoporosis. (2003). Prevention and Management of Osteoporosis: report of a WHO scientific group. In World Health Organization (Ed.). Geneva.

Yuksel, N., Majumdar, S. R., Biggs, C., & Tsuyuki, R. T. (2010). Community pharmacist-initiated screening program for osteoporosis: randomized controlled trial. Osteoporosis International, 21(3), 391-398. doi:10.1007/s00198-009-0977-z

3.2 Dietary intake of men with prostate cancer: a food group analysis.

This section describes the dietary intake of men with prostate cancer and survivors using a novel dietary method analysis. While the manuscript presented here assesses overall dietary intake, rather than osteoporosis-preventative dietary behaviours, this methodology was used to report on dairy products intake in section 3.1. This method was based on the food grouping system used to report on the diets of Australians in the National Nutrition and Physical Activity Survey (NNPAS) from the Australian Health Survey (AHS) (2011 - 2013). While food group analysis is not novel, the method and grouping system used to group the foods and comparison with the Australian population is novel. This is also new to the prostate cancer literature.

This manuscript was submitted to *Nutrition and Dietetics* and has been accepted pending changes. This manuscript has been peer-reviewed, changes made accordingly, and currently awaiting final approval by the editor.

Date of first submission: 22nd February 2015
Date re-submitted with changes: 9th June 2015

Please note that the reference style for this manuscript is that appropriate for the journal.

Maximising the richness of dietary data: a pilot study of the dietary intake of men with prostate cancer and prostate cancer survivors.

Annie-Claude M. Lassemillante1,2, Stephanie Hsu1, Tina Skinner3, John D. Hooper2, John B. Prins2,4, Olivia R. L. Wright1,2

Affiliations:

1 Centre for Dietetics Research (C-DIET-R), School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, QLD 4072, Australia.

2 Mater Research Institute – University of Queensland, Kent Street, Woolloongabba, QLD 4102, Australia.

3 Centre for Research on Exercise, Physical Activity and Health (CRExPAH), School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, QLD 4072, Australia.

4 The University of Queensland Diamantina Institute, The University of Queensland, Woolloongabba, QLD 4102, Australia.

Abstract

A reductionist approach, such as nutrient analysis, has been in dietary research, but it fails to acknowledge the multi-dimensional nature of diets. Food group analysis focuses on whole foods rather than specific nutrients. *Aim*: This pilot study aims to assess the food group intake of men with prostate cancer, and to compare this with the broader Australian population of men. *Method*: Diet history was collected from 41 men with prostate cancer. Foods were categorised using the Australian Health Survey (AHS) food categorisation system. The median weight of food group intake was compared between men with prostate cancer (n=41) and age-matched men from the National Nutrition Physical and Activity Survey (NNPAS). *Results*: Men with prostate cancer consumed 21 major food groups with “cereals and cereal products” contributing most to overall energy (20%; IQR 3-36%). “Meat, poultry, and game products and dishes” comprised 10% of overall energy and provided 12g/day of total fat intake (IQR 11g/day). The prostate cancer group consumed more “vegetable products and dishes” (303g/day vs 175g/day, $p<0.001$), less “alcoholic beverages” (107g/day vs 379g/day, $p<0.001$), “meat, poultry, and game products and dishes” (106g/day vs 150g/day, $p=0.007$), and “legumes and pulse products and dishes” (0g/day vs 161g/day, $p<0.001$) than their NNPAS counterparts. *Conclusion*: This methodology allowed to identify a range of eating behaviours that differed between

men with prostate cancer and Australian men, therefore highlighting the advantage of food group analysis over the reductionist approach. These findings combined with the current evidence can be used to guide nutrition advice in this group.

Keywords
Food; Food analysis; Nutrition assessment; Prostatic neoplasm

Introduction

The role of diet in prostate cancer risk and progression has been investigated in both clinical and epidemiological studies using a range of dietary analysis techniques;[1] however, findings are largely inconclusive.[1] Diet analysis has long used a reductionist approach in focussing on single nutrient intakes while ignoring the fact that diets are more complex and multi-dimensional.[2] Extensive studies in the prostate cancer field have also adopted this approach,[1, 3] but the results have been meagre. Such dietary analysis approach has allowed to identify the association of high saturated fat consumption with a greater risk of hormone-dependent cancer development and/or progression.[4] On the other hand, studies of lycopene from tomatoes have shown better outcomes on specific prostate cancer biomarkers when consumed as part of whole tomatoes or tomato paste, rather than lycopene supplements.[5]

Nutrient analysis is a valued part of nutrition research hierarchy, which also includes other global dietary assessments such as food group and dietary pattern analyses.[6, 7] Epidemiological studies have revealed the Mediterranean dietary pattern [8] may be protective against prostate cancer progression as a result of (i) its poly- and monounsaturated fat content,[9] and (ii) the synergy of all the nutrients and phytochemicals that form part of this diet.[10] This dietary pattern has also been extensively used in clinical trials, with positive results on disease outcomes.[11]

Food group analysis is valid, reliable, and detailed; and focuses on whole foods rather than specific nutrients.[6, 12] This method has an intuitive appeal because people primarily consume foods and dishes, which incidentally are sources of nutrients. Various methods of food group analyses have been used in research.[13, 14] Food groups can be devised using a theoretical approach;[15] a statistical approach, such as cluster analysis;[16] or by using an existing food grouping classification system. Depending on the patient population involved,

findings can be directly compared with a food guidance system, such as the Australian Dietary Guidelines (ADG)[17], to determine diet adequacy.

The majority of large studies investigating nutrition and prostate cancer prevention or survivorship rely on dietary data collection tools that are limited in their ability to capture the qualitative and quantitative complexity of diets through detailed and structured questioning of the study participants.[18] The food frequency questionnaire (FFQ) is often used to collect data on participants' intake of foods/nutrients thought to benefit cancer prevention or ameliorate its progression.[18] Studies using this dietary assessment tool often report precise amounts of food and/or nutrients and their relationship with disease,[19] which is not the intended use of the FFQ and compromises the validity of the findings.[20] Large population studies, such as the National Nutrition and Physical Activity Survey (NNPAS) [21] and NHANES 2013-2014[22], now prefer to collect dietary data at multiple time points using more detailed tools (for example, the 24-hour recall). There is, therefore, a need for valid and reliable diet analysis methods where extensive information can be drawn from the rich dietary data collected.[7]

This paper presents the results of a pilot study using an alternative food group analysis methodology. This post-hoc food group analysis was applied to a study in men with prostate cancer, originally designed to explore relationships between chronic health, diet, and bone health. The aim of this pilot study was to assess the detailed food group intake of a sample of men with prostate cancer utilising the same food group classification system as the NNPAS. These data were compared with the results for age-matched men from the NNPAS to identify their dietary similarities or differences. The methodology is different from previous dietary analysis methods as it takes into account the dietary habits and meal composition of Australians. This food grouping system has not previously been used in scholarly research and the results from such analysis can be directly compared with the wider Australian population to identify typical or atypical dietary behaviours.

Methods

Study participants: Participants for this pilot cross-sectional study were recruited from a student-led exercise program at The University of Queensland, Australia from September 2013 to June 2014. Eligible participants were: prostate cancer survivors or men with a current prostate cancer diagnosis; aged over 60 years; either currently undergoing active treatment or not previously treated; not diagnosed with metastatic bone disease; free of

cardiovascular, musculoskeletal or metabolic disorders that would have prevented safe participation in exercise; and a body mass less than 150 kg. The study was approved by The University of Queensland Medical Research Ethics Committee (2013001160). All participants provided written informed consent before commencing the study.

Background data: Personal information, detailed medical and prostate cancer history, nutritional supplementation, and medication use were obtained via an interviewer-administered questionnaire.

Anthropometry and body composition: Height and body mass were measured using standard procedures to the nearest 0.1 cm and 0.1 kg, respectively. Waist and hip girth were measured using an anthropometric tape (Lufkin W606PM retractable steel tape; Cooper Tools), to the nearest 0.1 cm, while participants were wearing light clothing. These were measured according to the procedures outlined by the International Society for the Advancement of Kinanthropometry[23]. Body mass index (BMI; kg/m^2) and waist-to-hip ratio (WHR) were derived from these measurements. Percentage lean body mass and percentage fat mass were measured by dual-energy x-ray absorptiometry (DXA; Hologic QDR 4500w).

Dietary assessment: An Accredited Practising Dietitian collected participant usual dietary intake using a validated open-ended diet history questionnaire (see Appendix VII).[24] During this structured interview participants were asked to recall their diet over the previous week to collect detailed dietary data about usual meals, snacks, and beverages. The Dietitian used neutral probes to aid in recall. Food preparation and cooking practices, product types, brands, accompaniments, and serving sizes were also recorded. Life-size images of foods[25] were used to assist in quantifying serving sizes. Participants were probed for take-away and restaurant meals consumed over the past fortnight. This was followed by completion of a food checklist to ensure dietary details were not missed. A similar approach was used in NNPAS. Data were analysed using the dietary analysis program Foodworks 7 (version 7.0, Xyris Software, Australia) to calculate mean daily nutrient intakes. The food-nutrient database used was AUSNUT 2007 as the new database, AUSNUT 2011-13, had not yet been incorporated in the dietary analysis software at time of data entry. The ratio of energy intake (EI) to basal metabolic rate (BMR; EI:BMR)[26] was used to identify energy under-reporters, which was defined as an EI:BMR ratio < 0.9. The same cut-off value has been used in NNPAS[27].

Food groups: Food group analysis was performed for the diets of each participant and compared to the national medians, as reported in NNPAS, AHS.[28] This national survey used the AUSNUT 2011-13 food-nutrient database to code the foods consumed. This database was developed to reflect the current Australian food supply, and contains 5,740 foods and beverages each with a unique 8-digit code.[29] The first 2 digits of this code determine the major food group to which a food belongs, and the first 3 digits determine the sub-major group. Based on this coding convention there are 24 major food groups and 132 sub-major food groups that are collectively called the AHS food classification.[30] The diets of the current study participants were also analysed using AUSNUT 2011-13, where each food was coded accordingly using Microsoft Excel 2010 (version 14.0, Microsoft Corporation). These foods were then grouped into major and sub-major food groups according to the NNPAS/AHS coding convention, for each study participant. The total weight of each food group (major and sub-major) was calculated as well as its energy contribution (kilojoules [kJ] and percentage of total energy intake). Table 3.3 outlines the major and sub-major food groups investigated and consumed by men with prostate cancer (see Appendix VIII for examples of foods in major and sub-major food groups). Cereal-type foods are grouped into two different categories, (i) “cereals and cereal products”, which includes wholemeal and refined breads, breakfast cereals, flours, and dry pasta; and (ii) “cereal based products and dishes”, which includes processed cereal products such as cakes, pies, and other baked products. The complete list of the constituents of the AHS food groups can be found elsewhere.[30] One serve of “alcoholic beverages” was defined as containing 10 g of alcohol[31] and compared to the alcohol intake recommendations outlined in the ADG.[17]

Statistical analysis: A minimum of 31 participants were needed to estimate the mean energy intake (kJ/day) of this sample (SD 2100 kJ/day[32] and marginal error 750 kJ/day).[33] Normally distributed variables (as per Shapiro-Wilks test) were reported as mean ± SD, and variables not normally distributed were reported as median (interquartile range [IQR]). Food group intake and their macro-nutrients contribution were reported as median (range) to demonstrate the true intake of this sample. Independent samples t-tests and Mann-Whitney tests were used to compare food group intake between energy under-reporters and the rest of the sample. Wilcoxon signed rank tests were used to determine whether the median food group intake of men with prostate cancer differed to the national population medians reported in the NNPAS. Statistical analyses were completed using Statistical Package for the Social Sciences (SPSS) software (version 22, IBM).

Table 3.3 Major and sub-major food groups consumed by men with prostate cancer

Major food group	Sub-major food groups
Non-alcoholic beverages	Tea
	Coffee and coffee substitutes
	Fruit and vegetable juices, and drinks
	Cordials
	Soft drinks, and flavoured mineral waters
	Other beverage flavourings and prepared beverages
Cereals and cereal products	Flours and other cereal grains and starches
	Regular breads, and bread rolls (plain/unfilled/untopped varieties)
	English-style muffins, flat breads, and savoury and sweet breads
	Pasta and pasta products (without sauce)
	Breakfast cereals, ready to eat
	Breakfast cereals, hot porridge style
Cereal based products and dishes	Sweet biscuits
	Savoury biscuits
	Cakes, muffins, scones, cake-type desserts
	Pastries
	Mixed dishes where cereal is the major ingredient
	Batter-based products
Fats and oils	Butters
	Dairy blends
	Margarine and table spreads
	Plant oils
Fish and seafood products and dishes	Fin fish (excluding commercially sterile)
	Crustacea and molluscs (excluding commercially sterile)
	Packed (commercially sterile) fish and seafood
	Fish and seafood products (homemade and takeaway)
	Mixed dishes with fish or seafood as the major component
Fruit products and dishes	Pome fruit
	Berry fruit
	Citrus fruit
	Stone fruit
	Tropical and subtropical fruit
	Other fruit
	Mixtures of two or more groups of fruit
	Dried fruit, preserved fruit
Egg products and dishes	Eggs
	Dishes where egg is the major ingredient
Meat, poultry and game products and dishes	Beef, sheep and pork, unprocessed
	Poultry and feathered game
	Sausages, frankfurts and saveloys
	Processed meat

	Mixed dishes where beef, sheep, pork or mammalian game is the major component
	Mixed dishes where poultry or feathered game is the major component
Milk products and dishes	Dairy milk (cow, sheep and goat)
	Yoghurt
	Cream
	Cheese
	Frozen milk products
	Custards
	Other dishes where milk or a milk product is the major component
	Flavoured milks and milkshakes
Dairy and meat substitutes	Dairy milk substitutes, unflavoured
	Soy-based yoghurts
Soup	Soup, homemade from basic ingredients
	Canned condensed soup (unprepared)
	Soup, commercially sterile, prepared from condensed or sold ready to heat
Seed and nut products and dishes	Seeds and seed products
	Nuts and nut products
Savoury sauces and condiments	Gravies and savoury sauces
	Pickles, chutneys and relishes
	Salad dressings
	Dips
Vegetable products and dishes	Potatoes
	Cabbage, cauliflower and similar brassica vegetables
	Carrot and similar root vegetables
	Leaf and stalk vegetables
	Peas and beans
	Tomato and tomato products
	Other fruiting vegetables
	Other vegetables and vegetable combinations
	Dishes where vegetable is the major component
Legume and pulse products and dishes	Mature legumes and pulses
	Mature legume and pulse products and dishes
Snack foods	Potato snacks
	Corn snacks
	Other snacks
Sugar products and dishes	Sugar, honey and syrups
	Jam and lemon spreads, chocolate spreads, sauces
	Dishes and products other than confectionery where sugar is the major component
Confectionery and cereal/nut/fruit/seed bars	Chocolate and chocolate-based confectionery
	Fruit, nut and seed-bars
	Muesli or cereal style bars

	Other confectionery
Alcoholic beverages	Beers
	Wines
	Spirits
	Cider and perry
Special dietary foods	Formula dietary foods
Miscellaneous	Yeast, and yeast vegetable or meat extracts

Results

Fifty-four men with prostate cancer were invited to participate in this study. A total of 41 men with prostate cancer and survivors were included, 12 declined to participate, and one was excluded as he did not meet the inclusion criteria. The characteristics of the study participants are presented in Table 3.4.

Disease and treatment characteristics

The sample comprised prostate cancer survivors and men currently undergoing treatment (26.8%, n = 11). All the men reported on their prostate cancer stage (past or present), with 58.5% (n = 24) reporting localised disease, 17% (n = 7) reporting advanced disease, and the remaining 10 participants could not recall their disease stage. Radical prostatectomy was common (58.5%, n = 24), and was either used in conjunction with other treatments (9.8%, n = 4) or used in isolation (48.8%, n = 20). Twenty study participants (48.8%) reported a form of radiation therapy as part of their prostate cancer treatment, including 12.2% (n = 5) receiving adjuvant radiotherapy.

Dietary characteristics

The EI:BMR ratio revealed that 9.8% (n = 4) of the study sample were energy under-reporters, which was lower than in NNPAS (19%)[34]. Energy under-reporters had a higher BMI ($P < 0.05$), hip circumference ($P < 0.05$), and body fat percentage ($P < 0.05$) than the rest of the sample. Dietary protein ($P < 0.05$), fat ($P < 0.05$) and carbohydrate intakes ($P < 0.05$) were lower in energy under-reporters. The intake of “sugar products and dishes” was also lower in this subset of the study participants. Energy under-reporters were not excluded from the analyses presented here to maintain consistency with the NNPAS results, which also did not exclude energy under-reporters.

Table 3.4 Participant characteristics and average macro-nutrients intake

Variable	All (n = 41)	95% confidence interval
Age, years	70.5 ± 5.3	68.8 – 72.2
Body mass, kg	82.6 ± 10.3	79.2 – 85.9
Height, cm	176 ± 5.57	174.6 – 178.2
BMI, kg/m^2	26.5 ± 3.2	25.5 – 27.5
BMI **<25 kg/m^2, % (n)** **25-30 kg/m^2, % (n)** **>30 kg/m^2, % (n)**	 36.6 (15) 46.3 (19) 17.1 (7)	-
Time since diagnosis, years	4.0 (6.5)	1 - 18[a]
Waist-to-hip ratio	0.98 (0.11)	0.8 – 1.9[a]
Percent fat mass	30.8 ± 5.1	29.3 – 32.5
Percent lean body mass	66.1 ± 5.0	64.4 – 67.6
Average energy intake, kJ/day	9100 ± 2300	8330 – 9840
Average protein intake, g/day **% energy intake**	95 ± 22 17.9 ± 2.7	87 – 102 17 – 18
Average carbohydrates intake, g/day **% energy intake**	210 ± 125 40.7 ± 7.6	201 – 253 38 – 42
Average fat intake, g/day **% energy intake**	75 ± 30 32.1 ± 8.6	71 – 91 30 – 35
Average fibre intake, g/day	30 ± 11	27 – 34

All values for continuous variables are presented as mean ± SD or presented as

Food group classification, energy, and macro-nutrients contribution

The complete AHS food grouping classification system includes culturally and age appropriate foods, for example “reptiles, amphibia, and insects” and “infant formulae and foods”; however, these were not consumed by men in this sample. Our study sample consumed 21 major food groups, with “cereals and cereal products” contributing the most to their energy intake (see Table 3.5). Daily energy intake ranged from (8200kJ/day and 14 800 kJ/day), with carbohydrates providing the greatest proportion of energy. The average fat, and protein intakes of the study participants were within the acceptable macro-nutrients distribution ranges;[35] however, carbohydrate intake was below or at the lower end of the recommended range. Given the association between fat, particularly saturated fat,[4] with the development and progression of hormone-related cancers, results for this macro-nutrient are presented in more detail here. The “Vegetable products and dishes” and “fruit products and dishes” groups are also described in detail due to their association with reduced rates of prostate cancer development and progression.[36, 37]

Table 3.5 Average daily macro-nutrients contribution from major food groups (and intake of sub-major food groups), ordered by energy contribution and contributing ≥ 5% of energy, consumed by men with prostate cancer.

	Percent energy	Carbohydrates (g/day)	Total fat (g/day)	Protein (g/day)
Cereals and cereal products	20 (3 - 36)	72 (0 – 155)	6 (0 - 18)	13 (0 - 30)
Regular breads, and bread rolls (plain/unfilled/untopped varieties)		32 (0 - 90)	3 (0 - 15)	7 (0 - 17)
Breakfast cereals, ready to eat		19 (0 - 66)	1 (0 - 14)	3 (0 - 11)
Flours and other cereal grains and starches		4 (0 - 86)	<1 (0 - 12)	<1 (0 - 16)
Meat, poultry and game products and dishes	10 (2 - 22)	<1 (0 - 38)	12 (3 - 38)	22 (5 - 56)
Poultry and feathered game		-	3 (0 - 19)	7 (0 - 25)
Beef, sheep and pork, unprocessed		-	4 (0 - 20)	9 (0 - 33)
Processed meat		0 (0 - 3)	1 (0 - 8)	2 (0 - 28)
Milk products and dishes	9 (0 - 32)	12 (0 - 85)	10 (0 - 41)	12 (0 - 42)
Dairy milk (cow, sheep and goat)		7 (0 - 36)	2 (0 - 19)	5 (0 - 28)
Cheese		-	5 (0 - 24)	4 (0 - 34)
Yoghurt		2 (0 -11)	<1 (0 - 7)	1 (0 - 10)
Cereal based products and dishes	9 (0 - 37)	20 (0 - 140)	5 (0 - 43)	4 (0 - 76)
Sweet biscuits		1 (0 - 116)	<1 (0 - 35)	<1 (0 - 10)
Savoury biscuits		1 (0 - 20)	<1 (0 - 4)	<1 (0 - 3)
Fruit products and dishes	7 (0 - 20)	34 (0 - 100)	<1 (0 – 3)	2 (0 - 79)
Vegetable products and dishes	7 (2 - 24)	16 (4 - 54)	3 (0 – 24)	5 (1 - 18)
Other fruiting vegetables		2 (0 - 12)	<1 (0 - 23)	1 (0 - 11)
Potatoes		7 (0 - 30)	<1 (0 - 6)	1 (0 - 7)
Tomato and tomato products		1 (0 - 4)	<1 (0 – 1)	<1 (0 - 2)
Carrot and similar root vegetables		2 (0 - 29)	<1 (0 – 3)	<1 (0 - 5)
Cabbage, cauliflower and similar brassica vegetables		<1 (0 - 3)	<1 (0 – 3)	1 (0 - 6)
Leaf and stalk vegetables		<1 (0 – 1s)	-	<1 (0 – 2)
Peas and beans		<1 (0 - 5)	-	<1 (0 - 4)

All values for continuous variables are presented as median (range).

Fat

"Fats and oils", consumed mostly in the form of "butters", contributed to 2% of their overall energy intake (range 0 – 31%) and provided 3 g/day of total fat intake (0 - 85 g/day). "Meat, poultry, and game products and dishes" contributed to 10% of their overall energy intake (range 2 - 22%) but provided 12g/day of total fat intake (range 3 - 38 g/day); therefore this food group was also a major source of saturated fats. "Milk products and dishes" was a significant source of fat (median total fat intake 10 g/day [range 0 - 41 g/day]), which was driven by the consumption of "cheese" (median total fat intake 5 g/day [range 0 – 24 g/day]). Further analyses revealed that about half of "dairy milk (cow, sheep and goat)" and "yoghurt" were either reduced or low in fat.

Men with prostate cancer consumed little "fish and seafood products and dishes" (median weight 23 g/day [range 0 - 129 g/day]), which contributed to 3 g/day of total fat (range 0 - 24 g/day). This major food group was further analysed to identify the intake of oily fish by men with prostate cancer. The median proportion of oily fish consumed by this sample was 83.9% (range 0 - 100%).

Vegetables and fruits

"Vegetable products and dishes" contributed to 7% (range 2 - 24%) of energy intake and was the second most consumed major food group, after "non-alcoholic beverages" (median weight 303 g/day [range 73 - 553 g/day] v/s 875 g/day [range 0 – 2557 g/day]). Analysis of sub-major food groups revealed that the proportion of "vegetable products and dishes" consumed as "other fruiting vegetables" (e.g. pumpkin) was 20.0% (range 0 - 38%) followed by "potatoes" 18.6% (range 0 - 58%), "tomato and tomato products", "carrots and similar root vegetables", and "cabbage, cauliflower, and other brassica vegetables". Overall "fruit products and dishes" was the fourth most consumed major food group, and consisted of 33.3% (range 0 – 90.5%) "pome fruits" and 17.8% (range 0 - 100%) "tropical and sub-tropical fruits".

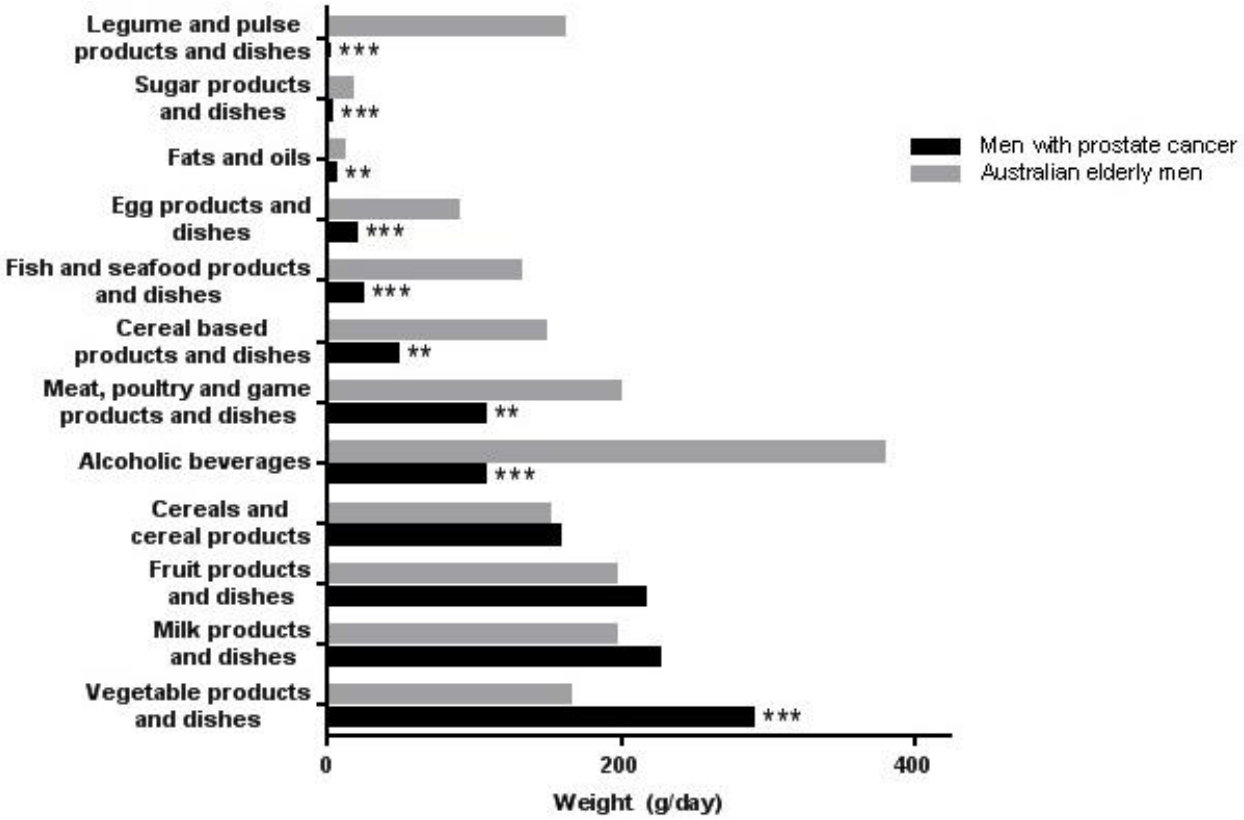
Comparison of food group intake with the Australian population

Figure 3.2 depicts the intakes of selected major food groups by men with prostate cancer in comparison with AHS age-matched counterparts (see Appendix IX for actual intakes). Men with prostate cancer consumed more "vegetable products and dishes" than the national average (303 g/day for men with prostate cancer vs 175 g/day for AHS men). Men in this study consumed less "potatoes" than men in the AHS group (40 g/day vs 126 g/day,

p < 0.001). This sample also consumed less “carrots and similar root vegetables” than the AHS men (25 g/day vs 60 g/day, p=0.012), while no differences in consumption of “tomato and tomato products” and “cabbage, cauliflower, and similar brassica vegetables” were observed (30 g/day vs 30 g/day, p = 0.183; and 22 g/day vs 38 g/day, p = 0.149 and respectively).

The three animal protein food groups such as “egg products and dishes”, “fish and seafood products and dishes”, and “meat, poultry and game products and dishes” were consumed in lesser amounts by men with prostate cancer than AHS group of men. Men with prostate cancer also consumed less “processed meat” than AHS men (11 g/day vs 25 g/day, P = 0.001).

Figure 3.2 Intake of selected major food groups by men with prostate cancer in comparison with elderly men from the Australian Health Survey.



Statistically significant difference **P ≤ 0.01, or ***P ≤ 0.001 when both groups are compared.

The difference in “non-alcoholic beverages” intake between men with prostate cancer (median consumption 875 g/day) and the AHS men (median consumption 1250 g/day) can be explained by “water” not included in the total “non-alcoholic beverages” intake of the men with prostate cancer. The men in this study also consumed less “alcoholic beverages”

than their AHS counterparts (107 vs 379 g/day, P < 0.001). Men with prostate cancer consumed a median of 1 standard drinks per day (range 0 – 8 standard drinks per day), which are within the ADGs recommendation to reduce risk of chronic disease from alcohol intake.[17] It is important to note that participants above the 50th percentile are likely to exceed these recommendations.

Discussion

This is the first study to pilot the use of the AHS food classification in dietary analysis research, and to analyse the diets of men with prostate cancer. It is also the first study to use the existing AHS food intake data to serve as a control for a study sample. No previous studies have profiled the food intake of men with prostate cancer and survivors in this level of detail.

We report that a sample of men with prostate cancer generally have healthier eating behaviours than an age-matched sample of AHS elderly men. This methodology has allowed for a detailed description of the diets of men with prostate cancer beyond macro-nutrient intakes. We identified differences in major food groups but also differences in sub-major food groups that illustrate how this methodology can be used in nutrition research. Men with prostate cancer consumed significantly more vegetables (major food group) than their AHS counterparts, which could be a result of modification to healthier dietary habits after cancer diagnosis.[38] The AHS classification system allowed a more detailed exploration of vegetable intake based on their nutritional properties (at the sub-major food group level),[30] for example grouping based on health-enhancing phytochemicals. This is demonstrated by the fact that “cabbage, cauliflower and similar brassica vegetables” are rich in glucosinolates, which have been associated with reducing prostate cancer risk and progression[39-41]. Meaningful inferences can therefore be drawn when using this food group analysis compared to the generic five food groups traditionally used in Australia to assess diet quality and adequacy.[17] As a result of the high phytochemical nutrient density of brassica vegetables,[42] we may have expected to see differences in the intake of this sub-major food group between men with prostate cancer and AHS men, but this was not observed.

Educating patients and the wider population about the diet-disease relationship is central to dietetic practice; however, the reductionist approach that dominates nutrition research only addresses the nutrient-disease relationship. Food group analysis allows a broader

investigation of food-disease relationships, therefore assisting practitioners to make judgements about diet quality and how it may be associated with the disease of interest, thereby encompassing a more practical and holistic approach to dietetic practice. Layering nutrient intakes on top of food group intake provides another dimension to this analysis. It is valuable to know the sources of certain nutrients either for hypothesis formulation or developing recommendations.

When looking at the energy intake of our sample we can conclude that they are not consuming excess energy; but some of their dietary habits could be detrimental to their health. For example, food group analysis of our pilot study participants revealed that "meat, poultry, and game products and dishes" was the second major source of energy and contributed the most to total fat intake. This shows the fat profile of our sample was not optimal with regard to poly- and monounsaturated fats and reveals an area for dietary intervention to promote cardiovascular health, which may already be compromised due to prostate cancer treatment. [43] Men in our sample consumed more "vegetable products and dishes" than their AHS counterparts, but did not meet the ADG recommendations[17] (~3 serves [289 g/day] instead of 5 serves [375 g/day]), nor did they meet the Mediterranean diet recommendations of more than 2 serves per meal.[44] This is a concern for men with prostate cancer as they are at elevated risk of being diagnosed with metabolic syndrome because of cancer treatment[43] and older age.[45] Comparisons between the diets of men with prostate cancer and the Mediterranean diet pattern are more appropriate than comparisons with the ADGs. This is because the latter recommendations are for chronic disease prevention[17] while the Mediterranean diet has been proven to be effective chronic disease management,[11] which is prevalent in men with prostate cancer and survivors.[43] Therefore by looking at their diets more globally we can make the recommendation to decrease "meat, poultry and game products and dishes" intake while increasing "vegetable products and dishes" , and "fish and seafood products and dishes" to be in line with the Mediterranean pattern of eating which is known to reduce the risk of metabolic syndrome.[46]

One shortfall of the AUSNUT 2011-13 database is that foods are not classified by their fat type or content, for example low fat dairy products and oily fish groups are not included. This can be overcome by analysing the respective major or sub-major food groups for specific nutrient content as illustrated in our analysis of the intake of oily "fish and seafood products and dishes", and low and reduced fat "milk products and dishes". This additional

analysis would be important for studies examining conditions where substantial evidence suggests a link between a specific nutrient and health/food (for example unsaturated fats and chronic health).[47] A limitation of this study was the low consumption of “soups” and “legume pulse products and dishes” that resulted in significant differences between the AHS group of men, and could have been a result of seasonality. The use of two different food-nutrient databases to report on the macro-nutrient intake and food group intake is a limitation of this study, but is likely to be resolved with updated versions of Foodworks, which will include AUSNUT11-13 hence streamlining food group analysis. The sample size of this study is small, and may include some bias due to inherent flaws associated with research volunteers; hence the results presented here cannot be generalised to the prostate cancer population.

A strength of this study protocol is that the diet history was collected by a Dietitian who was able to gather vital information about composite dishes consumed by the study participants. These dishes were then disaggregated into ingredients that were grouped accordingly, hence providing more accurate information about nutrient contributions for each food group.[48] The accuracy of the dietary data collected is limited by the recall ability of the current study participants, but this is common to all dietary methods.[20] This is pertinent to men with prostate cancer, who might have some cognitive impairments secondary to advanced age and treatment-related side-effects.[49] Despite these limitations, the dietary data collection method used here remains more reliable than the majority of others used in this patient population, which rely on recall of food intake over the past year.[50] We implemented many safeguards to maximise recall, and these include use of neutral probes and visual aids. Many significant differences in major and sub-major food groups intake observed between AHS men and men with prostate cancer could be a product of the lack of cultural diversity in our sample. Although the sample size was small and cannot be generalised to the prostate cancer population, it does not undermine the illustrative and descriptive purposes of this paper. Future research into dietary behaviours of men with prostate cancer should therefore include men at different stage on the prostatic disease continuum (prostate cancer and men with BPH) and healthy controls. The comparison of such findings with population data will reveal the dietary similarities between men with diseased prostates and healthy controls, thus indicating whether healthy diet messages should be targeted or universal.

Food grouping analyses are labour-intensive and time-consuming. Using food groups from an existing national database such as AUSNUT11-13, which can then be incorporated in food analysis software, will facilitate this process.[51] Focussing on intakes of food groups, rather than the reductionist approach, acknowledges the multi-dimensional aspects of diets. Food group analysis is versatile in that it can be applied to a range of studies, from epidemiologic to randomised controlled trials. Most importantly research on food groups, dietary patterns, and nutrient profiles complement each other; therefore, facilitating the translation to practical recommendations in medical nutrition therapy. This pilot study serves as a guide for further studies across all areas of dietetics practice to strengthen understanding of food behaviours in the context of whole diets.

References

1 Wright OR, Bauer JD, Lassemillante A-CM. Nutrition and Prostate Cancer: Latest Insights and Practice Recommendations. Cancer Forum. 2011; 35: [107]-[11].

2 Messina M, Lampe JW, Birt DF, et al. Reductionism and the Narrowing Nutrition Perspective: Time for Reevaluation and Emphasis on Food Synergy. J Am Diet Assoc. 2001; 101: 1416-19.

3 Masko EM, Allott EH, Freedland SJ. The Relationship Between Nutrition and Prostate Cancer: Is More Always Better? Eur Urol. 2013; 63: 810-20.

4 Pelser C, Mondul AM, Hollenbeck AR, Park Y. Dietary Fat, Fatty Acids, and Risk of Prostate Cancer in the NIH-AARP Diet and Health Study. Cancer Epidemiology Biomarkers & Prevention. 2013; 22: 697-707.

5 Wei MY, Giovannucci EL. Lycopene, Tomato Products, and Prostate Cancer Incidence: A Review and Reassessment in the PSA Screening Era. J Oncol. 2012; 2012: 7.

6 Jacobs DR, Tapsell LC. Food, Not Nutrients, Is the Fundamental Unit in Nutrition. Nutr Rev. 2007; 65: 439-50.

7 Jacobs D, Tapsell LC, Temple N. Food synergy: the key to balancing the nutrition research effort. Public Health Rev. 2012; 33: 1-23.

8 Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: A systematic review and meta-analysis of observational studies. Int J Cancer. 2014; 135: 1884-97.

9 Schröder H. Protective mechanisms of the Mediterranean diet in obesity and type 2 diabetes. J Nutr Biochem. 2007; 18: 149-60.

10 Jacobs DR, Tapsell LC. Food synergy: the key to a healthy diet. Proc Nutr Soc. 2013; 72: 200-6.
11 Kastorini C-M, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The Effect of Mediterranean Diet on Metabolic Syndrome and its Components: A Meta-Analysis of 50 Studies and 534,906 Individuals. J Am Coll Cardiol. 2011; 57: 1299-313.
12 Jacobs DR, Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy. The American Journal of Clinical Nutrition. 2003; 78: 508S-13S.
13 Mann N, Ashton Y, O'Connell S, Sinclair A, Kelly F. Food group categories used in dietary analysis can misrepresent the amount and type of fat present in foods. Nutr Diet. 2006; 63: 69-78.
14 Rangan A, Hector D, Randall D, Gill T, Webb K. Monitoring consumption of 'extra' foods in the Australian diet: Comparing two sets of criteria for classifying foods as 'extras'. Nutr Diet. 2007; 64: 261-67.
15 Grafenauer SJ, Tapsell LC, Beck EJ, Batterham MJ. Changes in food choice patterns in a weight loss intervention. Nutr Diet. 2015: n/a-n/a.
16 Burden S, Probst YC, Steel DG, Tapsell LC. Identification of food groups for use in a self-administered, computer-assisted diet history interview for use in Australia. J Food Compost Anal. 2009; 22: 130-36.
17 National Health and Medical Research Council. Australian Dietary Guidelines. Canberra: National Health and Medical Research Council, 2013.
18 Dagnelie PC, Schuurman AG, Goldbohm RA, Van Den Brandt PA. Diet, anthropometric measures and prostate cancer risk: a review of prospective cohort and intervention studies. BJU Int. 2004; 93: 1139-50.
19 Wilson KM, Shui IM, Mucci LA, Giovannucci E. Calcium and phosphorus intake and prostate cancer risk: a 24-y follow-up study. The American Journal of Clinical Nutrition. 2015; 101: 173-83.
20 Gibson RS. Principles of nutritional assessment. New York: Oxford University Press, 2005.
21 Australian Bureau of Statistics. Australian Health Survey: Food Model Booklet. ACT: Australian Bureau of Statistics,, 2010.
22 Prevention CfDCa. Measuring guides for the Dietary Recall Interview. 2010. (Also available from:

http://www.cdc.gov/nchs/nhanes/measuring_guides_dri/measuringguides.htm, accessed 12 May 2015).

23 Stewart A., Marfell-Jones M., Olds T., H. DR. International Standards for Anthropometric Assessment (ISAK): Lower Hutt, New Zealand, 2011.

24 Martin GS. The interviewer-administered, open-ended diet history method for assessing usual dietary intakes in clinical research: relative and criterion validation studies. University of Wollongong Thesis Collection: University of Wollongong, 2004; 204.

25 Williams T. This=that: a life-size photo guide to food serves. Toowong, Qld: Trudy Williams Nutrition & Dietetics, 2011.

26 Goldberg GR, Black AE, Jebb SA, et al. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. Eur J Clin Nutr. 1991; 45: 569-81.

27 Australian Bureau of Statistics. Australian Health Survey: Under-reporting in nurition surveys cat. no. 4363.0.55.001. 2014. (Also available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4363.0.55.001Chapter651512011-13, accessed 29th October 2014).

28 Australian Bureau of Statistics. Median amount of foods consumes (grams)(a): Major and sub-major food groups (b). In: Australian Health Survey: Nutrition first results - Foods and nutrients --A, cat no 43640DO006_20112012. Canberra: ABS, 2014.

29 Food Standards Australia New Zealand. Food Nutrient Database. 2013. (Also available from: http://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/foodnutrient/Pages/default.aspx, accessed 29th October 2014).

30 Food Standards Australia New Zealand. Classfication of foods and dietary supplements. 2013. (Also available from: http://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/classificationofsupps/Pages/default.aspx, accessed 29th October 2014).

31 National Health and Medical Research Council. Australian guidelines to reduce health risks from alcohol drinking. 2009.

32 O'Neill R, Haseen F, Murray L, O'Sullivan J, Cantwell M. A randomised controlled trial to evaluate the efficacy of a 6-month dietary and physical activity intervention for patients receiving androgen deprivation therapy for prostate cancer. J Cancer Surviv. 2015: 1-10.

33 Hajian-Tilaki K. Sample size estimation in epidemiologic studies. Caspian Journal of Internal Medicine. 2011; 2: 289-98.

34 Australian Bureau of Statistics. Under-reporting in nutrition surveys. 2014. (Also available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4363.0.55.001Chapter651512011-13, accessed 26 January 2015).
35 National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand. NHMRC: Department of Health and Ageing,, 2005.
36 Hardin J, Cheng I, Witte JS. Impact of consumption of vegetable, fruit, grain, and high glycemic index foods on aggressive prostate cancer risk. Nutr Cancer. 2011; 63: 860-72.
37 Richman EL, Carroll PR, Chan JM. Vegetable and fruit intake after diagnosis and risk of prostate cancer progression. Int J Cancer. 2012; 131: 201-10.
38 Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM. Riding the Crest of the Teachable Moment: Promoting Long-Term Health After the Diagnosis of Cancer. J Clin Oncol. 2005; 23: 5814-30.
39 Hayes JD, Kelleher MO, Eggleston IM. The cancer chemopreventive actions of phytochemicals derived from glucosinolates. Eur J Nutr. 2008; 47 Suppl 2: 73-88.
40 Kristal AR, Lampe JW. Brassica Vegetables and Prostate Cancer Risk: A Review of the Epidemiological Evidence. Nutr Cancer. 2002; 42: 1-9.
41 Steinbrecher A, Nimptsch K, Hüsing A, Rohrmann S, Linseisen J. Dietary glucosinolate intake and risk of prostate cancer in the EPIC-Heidelberg cohort study. Int J Cancer. 2009; 125: 2179-86.
42 Podsędek A. Natural antioxidants and antioxidant capacity of Brassica vegetables: A review. LWT - Food Science and Technology. 2007; 40: 1-11.
43 Collier A, Ghosh S, McGlynn B, Hollins G. Prostate Cancer, Androgen Deprivation Therapy, Obesity, the Metabolic Syndrome, Type 2 Diabetes, and Cardiovascular Disease: A Review. Am J Clin Oncol. 2012; 35: 504-09 10.1097/COC.0b013e318201a406.
44 Bach-Faig A, Berry EM, Lairon D, et al. Mediterranean diet pyramid today. Science and cultural updates. Public Health Nutr. 2011; 14: 2274-84.
45 Park Y, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the third national health and nutrition examination survey, 1988-1994. Arch Intern Med. 2003; 163: 427-36.
46 Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. 2008; 337.

47 Brazionis L, Ting E, Itsiopoulos C, Wilson A, Hodge A. The effects of fish or fish oil on the omega-3 index. Nutr Diet. 2012; 69: 5-12.

48 Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US 1989 to 1991. J Am Diet Assoc. 1998; 98: 537-47.

49 Nelson CJ, Lee JS, Gamboa MC, Roth AJ. Cognitive effects of hormone therapy in men with prostate cancer. Cancer. 2008; 113: 1097-106.

50 Dennis LK, Snetselaar LG, Smith BJ, Stewart RE, Robbins MEC. Problems with the Assessment of Dietary Fat in Prostate Cancer Studies. Am J Epidemiol. 2004; 160: 436-44.

51 Lentjes MAH, McTaggart A, Mulligan AA, et al. Dietary intake measurement using 7 d diet diaries in British men and women in the European Prospective Investigation into Cancer-Norfolk study: a focus on methodological issues. Br J Nutr. 2014; 111: 516-26.

CHAPTER 4 DISCUSSION AND IMPLICATIONS FOR FUTURE RESEARCH

4.1 Discussion

Bone health on the prostate cancer continuum

Throughout this thesis, the poor bone health of men with prostate cancer and men with BPH was discussed. The prevalence of poor bone health is presented on the prostate cancer continuum [Figure 4.1], with men affected by this condition regardless of where they are on that continuum. Osteoporosis is highly prevalent in this population but also varies greatly (between 9% and 53% for men on ADT, and 4% and 38% for hormone-naïve men with prostate cancer) (75, 76). While a high prevalence of poor bone health was expected in men on ADT, the wide spread prevalence was unexpected. The meta-analyses summarised such spread, with results from DOES and the pilot cross-sectional study further supporting this conclusion. The latter study was small (n=41) but was not unlike many studies investigating the bone health of men with prostate cancer (35, 104-110). The variation in the prevalence of osteoporosis has been discussed in both meta-analyses (see CHAPTER 1). The sensitivity analyses revealed that ethnicity, disease stage, and age were responsible for some of this variation. It is also possible that the different DXA machines used across the studies would account for some of the variance. The differences between the two most common DXA machines, Prodigy and Hologic, are known (111) and can range from 8.2% to 21.0%, with the largest difference seen at the femoral neck (112). The ROI used to assess overall bone health also impacts on the diagnosis of osteoporosis, which is likely due to the presence of osteo-dense regions at the lumbar spine, called osteophytes, leading to erroneously high BMDs (48, 113). Osteophytes are seen in elderly men with osteoarthritis of the lumbar spine (48, 114), which is a common degenerative condition in this gender. Lumbar spine BMD can be further elevated in men with prostate cancer from osteoblastic metastases (115, 116). The high frequency of spinal metastases in men with prostate cancer (115) can be explained by the venous circulation from the pelvic region to the vena cava through the vertebral venous system (117-119). The proximity of the vertebrae to this circulation system provides an ideal environment (the “soil” (6)) for circulating prostate cancer cells to home to. Therefore lumbar spine is not representative of overall bone health in elderly men and should be excluded from bone health examination protocols. This is of particular importance in men with prostate cancer who can have both osteophytes and osteoblastic metastases, therefore greatly affecting the validity of the lumbar spine in assessing their

bone health. The challenges of measuring BMD at the lumbar spine in men have not stopped this ROI from being used both in research (36, 104, 109, 120-123) and in practice (124, 125). It is therefore evident that osteoporosis diagnosis methods are tailored to women, and still need to be altered for accurate diagnosis in men. The forearm BMD has been shown to be representative of overall bone health in men (124), and it provides an alternative in assessing bone health in elderly men and those with prostate cancer. Unfortunately organisations such as the WHO and prostate cancer clinical guidelines do not recommend using the forearm instead of the lumbar spine (125, 126). Many studies investigating the bone health of men with prostate cancer exclude those with metastases at the lumbar spine (107, 123, 127) and fail to use an alternative ROI. This is not a solution-based practice that also excludes a potentially important prostate cancer population from being investigated. This suggests that more high quality research needs to be undertaken using ROIs other than the lumbar spine to provide strong evidence, which can be used in guidelines development.

While Figure 4.1 is a simplification of prostate cancer progression, it summarises the findings of this research program and evidence to date. Only a few studies have reported on the bone health of men at both ends of the continuum; therefore these numbers are anticipated to change with the release of new evidence. The number of prostate cancer survivors has increased (128) because of early detection (129) and improved treatment (130) but the rate of osteoporosis is expected to increase with more men potentially treated with ADT. New pharmacological approaches, such as intermittent-ADT, that lessen the severity of traditional ADT prescriptions may mitigate some of this deterioration in bone health (131). Consistent bone health monitoring in association with these novel treatments would be valuable to estimate whether they have fewer negative effects on bone health.

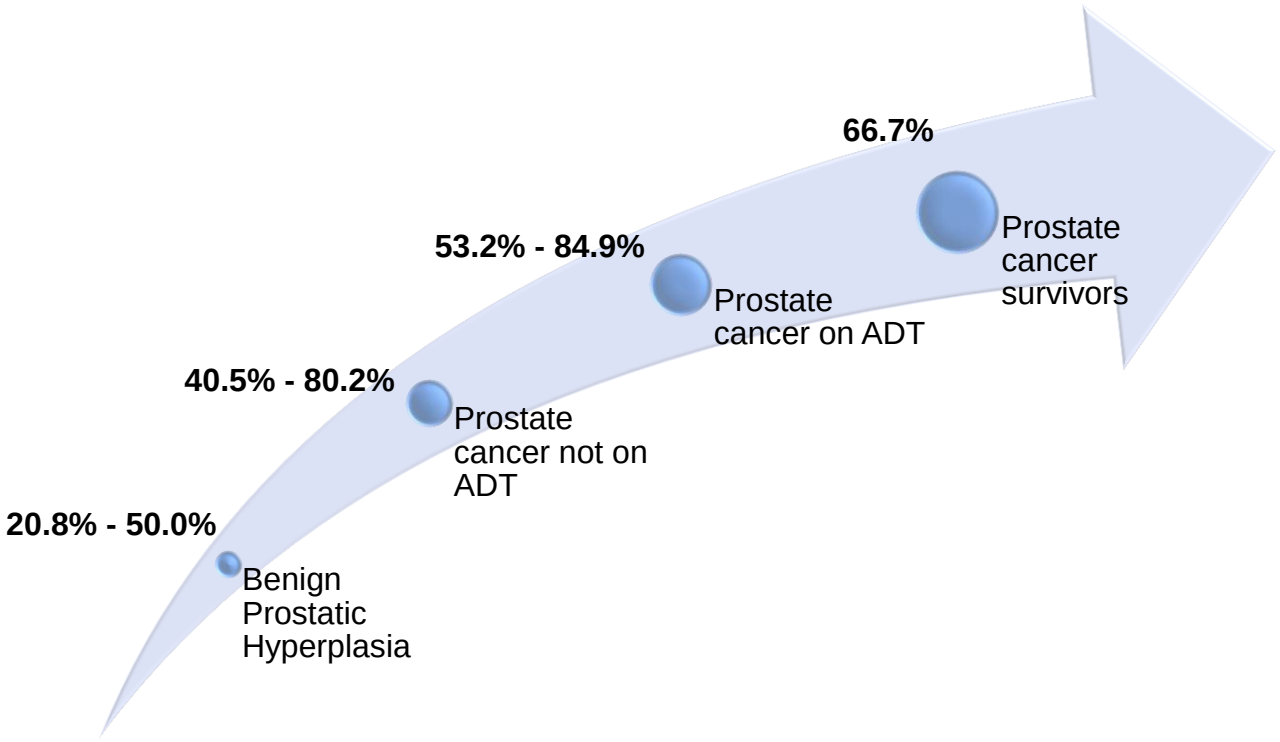


Figure 4.1 The prevalence of poor bone health (osteoporosis + low bone mass) on the prostate cancer continuum, regardless of bone site.

Osteoporosis and low bone mass have been combined for clinical relevance as risk of fractures increases with low bone mass in elderly men (132).

Implications of bone health management in men with prostate cancer

The release of new clinical guidelines in the USA and UK (94, 126) that include more comprehensive bone health management recommendations could positively impact the future bone health of men with prostate cancer and survivors. This impact is dependent on whether or not these guidelines are fully implemented by medical practitioners; hence future investigations into the extent of guideline implementation alongside specific clinical outcomes will provide information on their effectiveness. It is important to implement guidelines using theoretical frameworks to effect sustainable behaviour change (133, 134). The results from the cross-sectional study outline the role of psycho-behavioural and –social factors (individual theoretical constructs) in bone healthy behaviours among men with prostate cancer. Therefore future investigations using theoretical frameworks in guideline implementation will help to measure the translation of recommendations into behaviour change and clinical outcomes.

Prostate cancer survivors are a hormonally heterogeneous group comprising both men previously treated with ADT and not previously treated with ADT, but in this thesis they are considered to be past ADT-users. The bone health of men with prostate cancer is driven by treatment (75), possible disease pathophysiology (135-137), genes (138), and lifestyle (139). The mechanism underlying bone loss in men with prostate cancer has been discussed in section 1.3. In clinical practice, survivors are also likely to have poorer bone health than men with a current prostate cancer diagnosis due to bone loss associated with age (prostate cancer survivors are older) and treatment (including radiotherapy and ADT). Of all these different aetiologies, bone loss in men with prostate cancer on ADT is expected and is managed better when compared with the bone health of men with prostate cancer who are not on ADT (140, 141). The findings presented in this research program support the need to manage the bone health of all men with diseased prostates rather than focussing only on men being treated with ADT. There are two main advantages to implementing health promotion strategies for bones at every point on the prostate cancer continuum. These include:

- There is strong evidence that dietary calcium and supplemental calcium (65) reduce bone loss; therefore early intervention (prior to ADT initiation) will minimise bone loss in men with prostate cancer (mainly age-related bone loss). This strategy means men would start ADT with less depleted bones, which may help minimise the consequences associated with ADT. An example of a measurable outcome of this strategy is extending the time to fracture in this population (142), although more studies are needed this area. Men would have also formed long-term bone healthy habits, which will therefore be easier to maintain over time (143).

- Early intervention may reduce the economic burden of osteoporosis in men with prostate cancer. In 2011-2012, 40 289 claims for ADT (Goserelin and bicalutamide; and leuprolide) were made under the Pharmaceutical Benefits Schedule in Australia compared with 38 400 on 2008-2009 (24). Given this increase in the number of patients on ADT and that up to 85% of men on ADT have osteoporosis or osteopenia (76), there will be will be an increase in osteoporosis and/or fractures related costs, especially if bone health management strategies remain unchanged.

Health behaviours: the clinician's perspective

The results from the cross-sectional study describe some lifestyle aspects, notably diet, that affects this population. Men with prostate cancer and survivors, regardless of hormonal status, are not meeting their calcium requirements or consuming adequate amounts of dairy for optimum health. The NH&MRC osteoporosis guidelines/algorithm, recommends increasing dietary calcium intake to reduce bone loss (Grade A recommendation) (144); verifying the strong evidence to support the bone protective effects of dietary calcium (145). The combination of this poor dietary behaviour and the failure by medical practitioners to recognise that men with prostate cancer are at risk of osteoporosis (146) is concerning. Additionally, these men do not believe that osteoporosis is a serious disease as demonstrated in this research program. This has previously been summarised by Gaines and Marx (147), who also reported that men have a limited understanding of the osteoporosis disease process, risk factors, and prevention. Men in the cross-sectional study, presented in this thesis, had poor knowledge of the relationship between osteoporosis and men's health, as was seen in Gaines's review of the literature (147). These authors also found that men knew more about the female-osteoporosis relationship than they knew about the male-osteoporosis relationship (147).

Deficits in bone health knowledge, beliefs and perceptions, and bone health protective behaviours can be due to the treating doctor not discussing/recognising bone health issues with/in their patients (77, 146). A review of osteoporosis-specific knowledge among doctors (and other health professionals) revealed that they have good knowledge of osteoporosis diagnosis and management but poor knowledge on calcium-containing foods and recommended intake (86). The recently reviewed clinical guidelines on the management of prostate cancer (94, 126) provide details on bone health monitoring strategies as well as bone health management recommendations. These include specific calcium and vitamin D recommendations through supplementation and are likely to improve this aspect of care in men with prostate cancer. These recommendations emphasise the need for Dietitians to be included in bone health management efforts to bridge this gap in specific health behaviours knowledge and the implementation of dietary behaviour change. It is imperative that these guidelines be adopted in practice as the number of men with prostate cancer treated with ADT is increasing (24), thereby increasing the proportion of men with poor bone health and at increased risks for fractures.

Health behaviours: the importance of behavioural change theoretical frameworks

Understanding the reasons for the gap between knowledge and health behaviour and health status (among patients) is important as it will lead to the development of strategies to increase uptake of bone healthy behaviours among men with prostate cancer. Inadequate osteoporosis knowledge could play a role in the high prevalence of poor bone health in men with prostate cancer. According to Orem's Self-Care theory, one's knowledge of potential disease is a prerequisite for participating in health behaviours (88); therefore the lack of information on the deleterious effects of ADT on bone health, may result in poor participation in bone healthy behaviours. Education alone is not the solution to the osteoporosis problem as it may not be sufficient to change behaviour (148), therefore bone health education programs need to go beyond traditional osteoporosis interventions. These need to provide practical information that can be easily applied by men with prostate cancer as demonstrated in a study by Plawecki and Chapman-Novakofski (149). These authors (149) designed an eight-week group education program, whereby participants were educated on nutrition label reading, meal planning, and serving size estimation. This intervention led to increased calcium intake by the end of the study period, thus demonstrating the importance of providing such practical information. A recent osteoporosis intervention program in men with prostate cancer showed that increased osteoporosis knowledge and perceived susceptibility significantly improved intake of calcium and vitamin D (150). This intervention was one of the few among men with prostate cancer on ADT, and provided detailed written information including calcium-containing foods with practical information on how to incorporate them in their diets (150). While most of the bone healthy messages are targeted at men with prostate cancer on ADT, for obvious reasons, these messages should also reach hormone-naïve men with prostate cancer and men with BPH. Men not on ADT are also potential ADT candidates; therefore, encouraging implementation of behaviour change early at the time of diagnosis may reduce future risk for osteoporosis and fracture. Further studies are required to examine the impact of diet behaviour change from diagnosis on future risk of fracture in prostate cancer patients.

Educational Framework for Dietitians

Bone health management is shared between the nurse, medical team, allied health team, carer, and the patient (Figure 4.2). The findings presented here support the need for multidisciplinary management of bone health in men with prostate cancer; this is because behaviour change and enhanced self-efficacy in one type of health behaviour drive

behaviour and self-efficacy in another health behaviour. There is also evidence to suggest that a multidisciplinary education program enhances osteoporosis knowledge (151). Allied health professionals, such as Dietitians and Exercise Physiologists, therefore need to be familiar with the (i) iatrogenic effects of prostate cancer treatments, like the effects of ADT on chronic health and bone health, (ii) the management strategies of such side-effects, and (iii) the current fads (dietary) and health misinformation in the prostate cancer community. The multi-modal osteoporosis education intervention designed by Tussing and Chapman-Novakofski (152), demonstrates that Dietitians can deliver successful programs that lead to increased dietary calcium intake. This program was theory-based (Health Belief Model and Theory of Reasoned Action), thus suggesting the importance of such framework when designing and delivering education programs. Dietitians are trained in such theories, and use them to assess patient's current dietary behaviours and to tailor dietary intervention to the patient's circumstances and preferences (153).

Results from this research program and the literature support the lack of knowledge and perceived seriousness related to osteoporosis in men with prostate cancer. Reports on these constructs are common in the literature as the Health Belief Model is the most frequent theoretical framework used to investigate osteoporosis and health behaviours (83). In dietetic practice, the prostate cancer patient is likely to present with multiple comorbidities (e.g. metabolic syndrome and osteoporosis secondary to ADT); therefore Medical Nutrition Therapy needs to be carefully planned in order to address these many conditions. Because of the burden of prostate cancer, (uncertainty associated with active surveillance and devastating effects of ADT) men with prostate cancer can (i) partake in many food fads in an attempt to fight the cancer (154), or (ii) be overwhelmed by their diagnosis and have/gain insufficient knowledge about disease and diet. The Nutrition Care Process is a systematic approach used by Dietitians to provide Medical Nutrition Therapy (155). The findings presented in this thesis are used to design a framework, which is based in the Nutrition Care Process, for the management of bone health in men with prostate cancer and survivors. The assessment and diagnosis will differ between patients and it will guide the content of the intervention. This should be based on a counselling theoretical approach such as the Health Belief Model, which is ideal for osteoporosis counselling in men with prostate cancer as it is successful in group interventions (152). Table 4.1 presents a modified table from the Nutrition Care Process (156) to assist in osteoporosis counselling using the Health Belief Model. Information on metabolic syndrome can be added to this table for a holistic intervention on the side-effects of ADT.

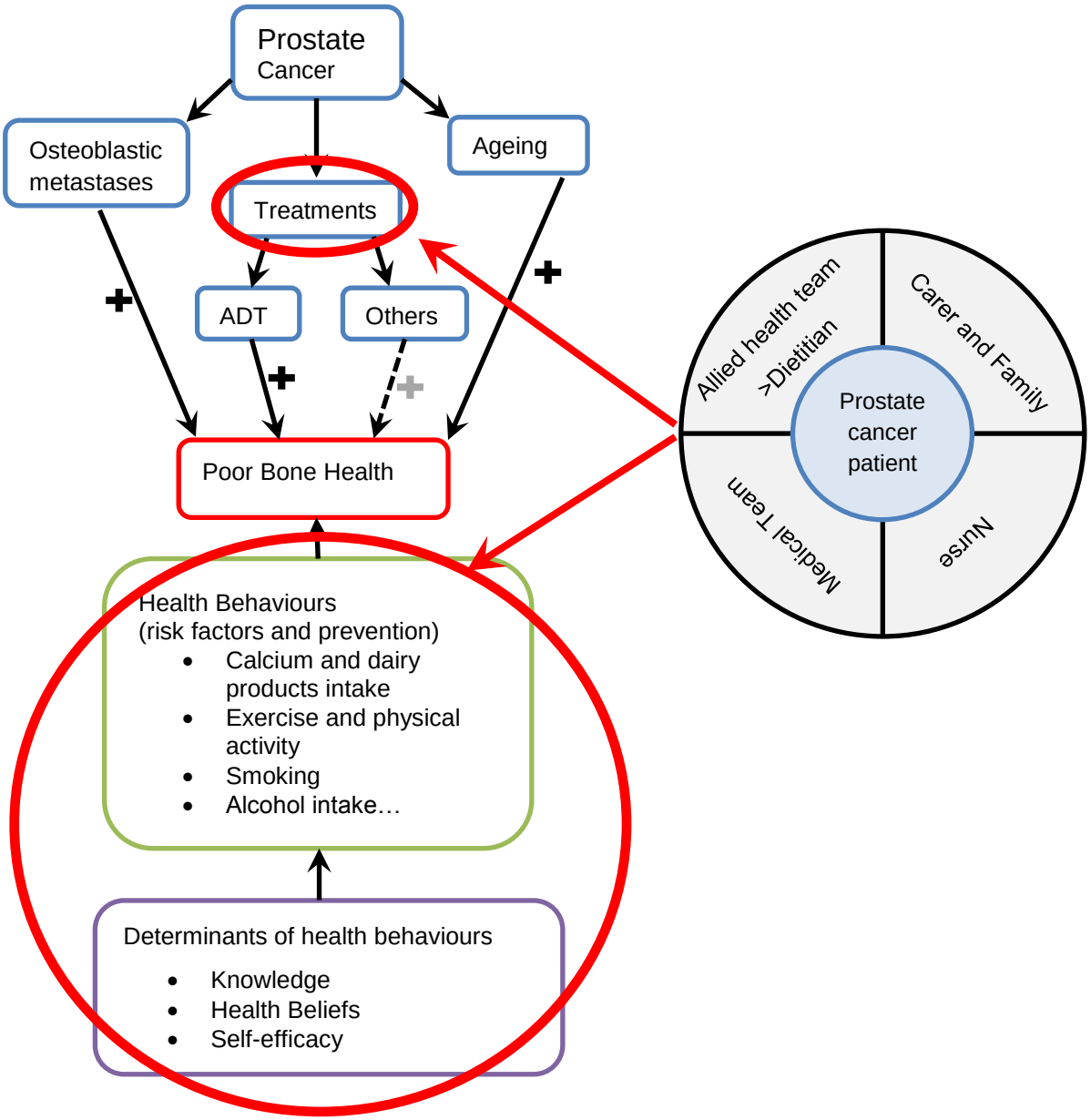


Figure 4.2 Theoretical framework mapping the involvement of the dietitian (and all involved in prostate cancer care) in behaviour change for the management of bone health in men with prostate cancer.

Table 4.1 How to apply the Health Belief Model in nutrition counselling of osteoporosis in men with prostate cancer.
This table is based on (156).

Construct	Definition	Strategies
Perceived Susceptibility	Client's belief or opinion of the personal threat **osteoporosis** represents for them; client opinion regarding whether they have **osteoporosis** or their chance of getting **osteoporosis**	• Educate on **osteoporosis** risk factors, e.g., low calcium intake, low dairy intake, excessive alcohol intake… • Tailor information to the client, more specifically to men and ADT (if applicable) • Ask client if they think they are at risk or have the **osteoporosis or poor bone health** • Guided discussions • Motivational interviewing (express empathy, open-ended questions, reflective listening, affirming, summarizing, and eliciting self-motivation statements)
Perceived Severity	Client's belief about the impact **osteoporosis** threat will have on them and their lifestyle	• Educate on consequences **osteoporosis or low bone mass**; show graphs and statistics of **fractures** and their impact on **quality of life** • Elicit client response • Discuss potential impact of **fractures** on client's lifestyle • Motivational interviewing
Perceived Benefits and Barriers	Client's belief regarding benefits they will derive from taking nutrition-related action (**increase vitamin D, calcium and/or dairy intake**); perceived benefits versus barriers - client's perception of whether benefits will outweigh the sacrifices and efforts involved in behaviour change	• Clearly define benefits of nutrition therapy and physical activity, e.g. **reducing bone loss** and **reduction in risk of fractures** • Role models, testimonials • Explore ambivalence and barriers • Imagine the future • Explore successes • Summarize and affirm the positive
Cues to Action	Internal or external triggers that motivate or stimulate action	• How-to education • Link current symptoms to **osteoporosis** • Discuss media information and fallacy that **osteoporosis** only affects women • Social support, e.g. prostate cancer support groups, osteoporosis support groups
Self-Efficacy	Client confidence in their ability to successfully accomplish the necessary action	• Skill training/demonstration, e.g., on how to **incorporate more dairy in the diet** and **how to increase calcium and vitamin D intake** • Introduce alternatives and choices, e.g., **calcium and vitamin D supplements** (brands, types and dosage) • Behaviour contracting; small, incremental goals • Coaching, verbal reinforcement

Table 4.2 Summary of research findings reported in this research program.

Research question/Aim	Outcome
To explore the literature on the prevalence of osteoporosis and/or low bone mass (osteopenia) in men with prostate cancer, whether treated with ADT or not on ADT	Up to 85% of men with prostate cancer on ADT and up to 80% of hormone-naïve men with prostate cancer experience poor bone health.
What are the bone-health management recommendations **made in** evidence-based guidelines **for the management of** prostate cancer**?**	Inconsistent recommendations across 4 evidence-based guidelines documents: all mention deleterious effects of ADT on bone health and most recommend bone health monitoring post ADT initiation.
Do the **recommendations include lifestyle management strategies,** such as increasing **dietary calcium** and **exercise/physical activity?**	3 out of 4 guidelines documents recommend • exercise for the management of osteoporosis in men with prostate cancer on ADT. • calcium and vitamin D for osteoporosis management.
If such **recommendations** are **made,** how **detailed** and **comprehensive** are they?	Only 1 guidelines document provided strong emphasis on osteoporosis preventative measures, including the involvement of a Nutritionists. 2 out of 4 refer to *Osteoporosis Guidelines* for detailed recommendations. Specific calcium and vitamin D dosages and exercise prescriptions were only included in 1 guidelines document.
What is **the post-diagnostic incidence** of **osteoporosis and/or low bone mass** in **men with BPH, men with prostate cancer on ADT, and hormone-naïve men with prostate cancer?**	Post-diagnostic incidence of osteoporosis in: • men with BPH was 20.8% (at lumbar spine) and 59.2% (at femoral neck) • hormone-naïve men with prostate cancer was 23.1% (at lumbar spine) and 50.0% (at femoral neck) • men with prostate cancer on ADT was 44.4% (at lumbar spine) and 51.9% (at femoral neck) The odds of having LS osteoporosis/osteopenia are 3.2 times lower in men with BPH than men with prostate cancer on ADT ($p = 0.035$).
What is the **rate of post-diagnostic fractures** in the population mentioned above?	Hazard ratio of post-diagnostic fractures lower in men with BPH when compared with men with prostate cancer on ADT (HR: 0.284, 95% CI = 0.091 - 0.892; $p = 0.031$).
What is the extent **of** osteoporosis knowledge**, osteoporosis-related** health beliefs**, and** self-efficacy **in men with prostate cancer and survivors?**	The majority of men with prostate cancer and survivors had inadequate osteoporosis knowledge, with an average FOOQ score of 43.3% (SD 18%). Men with prostate cancer and survivors did not perceive they were susceptible to osteoporosis or that it was a serious disease. Participants reported minimal barriers to exercise (in osteoporosis management) and rated the benefits of exercise (in osteoporosis management) highly.
What are the health behaviours**, notably dietary behaviours, that men with prostate cancer and survivors participate in?**	Calcium supplementation was reported by 19.5% (n = 8) of men and vitamin D supplementation in 26.8% (n = 11).

And are they adequate **for optimum bone health?**	22% of men with prostate cancer and survivors met their calcium requirements, even when taking calcium supplementation into account.
What is the **association between determinants of health behaviours (psycho-behavioural and psycho–social factors), and bone health; and dietary behaviours** in men with prostate cancer and survivors?	Osteoporosis knowledge was positively correlated with general health motivation ($\tau = 0.26$, $p = 0.05$) and perceived benefits of exercise ($\tau = 0.26$, $p = 0.05$), and negatively correlated with perceived barriers to calcium intake ($\tau = -0.47$, $p < 0.001$). There was a positive correlation between the perceived benefits of exercise and the perceived benefits of calcium intake ($\tau = 0.41$, $p = 0.003$).

4.2 Implications for future research and conclusion

Calcium and vitamin D supplementation are routinely recommended in conjunction with bisphosphonates in the bone health management of bone loss secondary to osteoporosis (126). Although this is routine practice (and is recommended in clinical guidelines) there is no evidence that these supplements alone reduce bone loss or osteoporotic fractures in men with prostate cancer on ADT (157). The lack of evidence in the form of clinical trials demonstrates a gap in nutrition intervention in men with prostate cancer, whether on ADT or not. It is hypothesised that the bone-related outcomes of a nutrition intervention would be different between men with prostate cancer on ADT and not on ADT due to the different bone loss mechanisms in each group. Because of this difference, bone-related nutrition intervention studies need to target all men on the prostate cancer continuum but divide them into well-characterised groups for each stage along the continuum. This will assist in clarifying individualisation of bone health management strategies in each prostate cancer patient group. Time will be a challenge for such studies as the clinical outcome of osteoporosis, fractures, takes years to occur.

Prior to investing time and money in long-term nutrition and lifestyle interventions in men with prostate cancer, smaller investigations in behaviour change are needed. Such interventions may include group education programs, which have been successful in increasing osteoporosis knowledge, medication adherence, and calcium intake in women (158, 159). The educational framework presented in the discussion can also be used in smaller scale intervention studies (one-on-one or small group intervention) to assess how lifestyle recommendations, delivered using a specific theoretical framework, are implemented by men with prostate cancer. Such findings can then be used for larger scale studies or longer duration.

Osteoporosis research in men with prostate cancer is still in its infancy, especially osteoporosis education and intervention. Although ADT is known to negatively impact the bone health of men with prostate cancer, few lifestyle intervention studies have been undertaken on this population. More studies are therefore warranted, and the interventions need to (i) be based on health behaviour theoretical frameworks, (ii) use a multidisciplinary approach, (iii) include men early on the prostate cancer continuum as well as survivors, (iv) use tools targeted at a male audience, and (v) provide practical information such as specific strategies on how to increase the calcium content of a meal. Nadler, Alibhaiet al.

(150) are one of the few authors who have implemented an osteoporosis education program in men with prostate cancer on ADT, but the program did not address most of the points mentioned above. This intervention was not tailored to each patient nor did it include different allied health professionals, hence these limitations can be used as learning opportunities when developing future intervention studies. Davison, Wiens et al. (160) have also implemented an education program to increase the dietary calcium intake of men with prostate cancer on ADT, which only included a few of the above-mentioned recommendations. The dietary intervention in this study was delivered by a Dietitian, but it was not based on a behaviour change theoretical framework (160). While this intervention did not result in increased dietary calcium intake, the authors reported on higher calcium intakes in men on ADT for less than one year compared to those on ADT for more than one year (160). This finding support the recommendations made in this thesis, where bone health preventative strategies need to be implemented early on the prostate cancer continuum. Both of these studies (150, 160) include valuable elements of osteoporosis education but the lack of effect observed support the importance of a holistic approach. Although more research is needed to identify the most effective health behaviour change strategies, current osteoporosis population health messages and programs, which are targeted at women, can be expanded to also include men. The findings from this research program (i) have contributed to increasing the understanding of various aspects of bone in men with diseased prostates, and (ii) interpretation in conjunction with findings from previous intervention studies (such as (150) and (160)), will help improve bone health and side-effect management in men with prostate cancer. This thesis also demonstrates that there is more to osteoporosis management than prescribing calcium and vitamin D supplements. Behaviour change is challenging for the patient, health practitioner, and researcher; therefore there is no “one size fits all” solution, instead interdisciplinary involvement is crucial in research and in practice.

REFERENCES

1. Australian Institute of Health and Welfare. Cancer in Australia: An overview 2014. Cancer series no 90. Canberra: AIHW; 2014.
2. Chang RT, Kirby R, Challacombe BJ. Is there a link between BPH and prostate cancer? Practitioner. 2012;256(1750):13-6, 2.
3. National Comprehensive Cancer Network (NCCN). NCCN guidelines for prostate cancer (version 1.2015) 2015 [updated 24 October 2014; cited 2015 10 March]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
4. Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, et al. Metastatic patterns of prostate cancer: An autopsy study of 1,589 patients. Hum Pathol. 2000;31(5):578-83.
5. Rana A, Chisholm GD, Khan M, Sekharjit SS, Merrick MV, Elton RA. Patterns of bone metastasis and their prognostic significance in patients with carcinoma of the prostate. BJU. 1993;72(6):933-6.
6. Paget S. The distribution of secondary growths in cancer of the breast. Lancet. 1889;133(3421):571-3.
7. Schneider A, Kalikin LM, Mattos AC, Keller ET, Allen MJ, Pienta KJ, et al. Bone turnover mediates preferential localization of prostate cancer in the skeleton. Endocrinology. 2005;146(4):1727-36.
8. Imbriaco M, Larson SM, Yeung HW, Mawlawi OR, Erdi Y, Venkatraman ES, et al. A new parameter for measuring metastatic bone involvement by prostate cancer: the Bone Scan Index. Clin Cancer Res. 1998;4(7):1765-72.
9. Jung K, Lein M, Stephan C, Von Hosslin K, Semjonow A, Sinha P, et al. Comparison of 10 serum bone turnover markers in prostate carcinoma patients with bone metastatic spread: Diagnostic and prognostic implications. Int J Cancer. 2004;111(5):783-91.
10. Jin JK, Dayyani F, Gallick GE. Steps in prostate cancer progression that lead to bone metastasis. Int J Cancer. 2011;128(11):2545-61.
11. Choueiri MB, Tu SM, Yu-Lee LY, Lin SH. The central role of osteoblasts in the metastasis of prostate cancer. Cancer Metast Reviews. 2006;25(4):601-9.
12. Brown JM, Vessella RL, Kostenuik PJ, Dunstan CR, Lange PH, Corey E. Serum osteoprotegerin levels are increased in patients with advanced prostate cancer. Clin Cancer Res. 2001;7(10):2977-83.

13. Holen I, Croucher PI, Hamdy FC, Eaton CL. Osteoprotegerin (OPG) is a survival factor for human prostate cancer cells. Cancer Res. 2002;62(6):1619-23.
14. Corey E, Brown LG, Kiefer JA, Quinn JE, Pitts TEM, Blair JM, et al. Osteoprotegerin in prostate cancer bone metastatis. Cancer Res. 2005;65(5):1710-8.
15. Mountzios G, Dimopoulos MA, Bamias A, Papadopoulos G, Kastritis E, Syrigos K, et al. Abnormal bone remodeling process is due to an imbalance in the receptor activator of nuclear factor-(kappa)B ligand (RANKL)/osteoprotegerin (OPG) axis in patients with solid tumors metastatic to the skeleton. Acta Oncol. 2007;46(2):221-9.
16. Logothetis CJ, Lin SH. Osteoblasts in prostate cancer metastasis to bone. Nat Rev Cancer. 2005;5(1):21-8.
17. Mundy GR. Metastasis: Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer. 2002;2(8):584-93.
18. Sone T, Tamada T, Jo Y, Miyoshi H, Fukunaga M. Analysis of three-dimensional microarchitecture and degree of mineralization in bone metastases from prostate cancer using synchrotron microcomputed tomography. Bone. 2004;35(2):432-8.
19. Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579-84.
20. Wallace M. Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. Oncol Nurs Forum. 2003;30(2):303-9.
21. Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JI, Partin AW, et al. Active surveillance program for prostate cancer: An update of the Johns Hopkins experience. J Clin Oncol. 2011;29(16):2185-90.
22. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol. 2010;28(1):126-31.
23. Chapple A, Ziebland S, Herxheimer A, McPherson A, Shepperd S, Miller R. Is ‘watchful waiting’ a real choice for men with prostate cancer? A qualitative study. BJU Int. 2002;90(3):257-64.
24. Medicare Australia Statistics Department of Human Services. Pharmaceutical Benefits Schedule Item Reports: Australian Government; 2015 [updated 25 February 2015; cited 2015 2 March]. Available from: http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp.
25. Denis LJ, Carnelro de Moura JL, Bono A, Sylvester R, Whelan P, Newling D, et al. Goserelin acetate and flutamide versus bilateral orchiectomy: a phase III EORTC trial

(30853). EORTC GU Group and EORTC Data Center. Urology. 1993;42(2):119-29; discussion 29-30.
26. Gomella LG. Effective testosterone suppression for prostate cancer: is there a best castration therapy? Reviews in urology. 2009;11(2):52-60.
27. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. JAMA. 2005;294(2):238-44.
28. Perez EA, M S, Durling FC, Weilbaecher K. Aromatase Inhibitors and Bone Loss. Oncology (Williston Park). 2006;20(9):1029-48.
29. Guise TA, Oefelein MG, Eastham JA, Cookson MS, Higano CS, Smith MR. Estrogenic side effects of androgen deprivation therapy. Reviews in urology. 2007;9(4):163-80.
30. Egerdie B, Saad F. Bone health in the prostate cancer patient receiving androgen deprivation therapy: a review of present and future management options. Canadian Urological Association Journal. 2010;4(2):129-35.
31. Shore ND, Crawford ED. Intermittent androgen deprivation therapy: Redefining the standard of care? Reviews in urology. 2010;12(1):1-11.
32. Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol. 2006;24(24):3979-83.
33. DiBlasio CJ, Malcolm JB, Derweesh IH, Womack JH, Kincade MC, Mancini JG, et al. Patterns of sexual and erectile dysfunction and response to treatment in patients receiving androgen deprivation therapy for prostate cancer. BJU Int. 2008;102(1):39-43.
34. Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. Urology. 2003;61(2, Supplement):32-8.
35. Wei JT, Gross M, Jaffe CA, Gravlin K, Lahaie M, Faerber GJ, et al. Androgen deprivation therapy for prostate cancer results in significant loss of bone density. Urology. 1999;54(4):607-11.
36. Morote J, Morin JP, Orsola A, Abascal JM, Salvador C, Trilla E, et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology. 2007;69(3):500-4.
37. Chang D, Joseph DJ, Ebert MA, Galvao DA, Taaffe DR, Denham JW, et al. Effect of androgen deprivation therapy on muscle attenuation in men with prostate cancer. J Med Imaging Radiat Oncol. 2014;58(2):223-8.
38. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature. 2003;423(6937):337-42.

39. Hamilton EJ, Ghasem-Zadeh A, Gianatti E, Lim-Joon D, Bolton D, Zebaze R, et al. Structural decay of bone microarchitecture in men with prostate cancer treated with androgen deprivation therapy. J Clin Endocrinol Metab. 2010;95(12):E456-E63.
40. Watts JJ, Abimanyi-Ochom. Julie, Sanders KM. Osteoporosis costing all Australians: A new burden of disease analysis - 2012-2022. NSW: 2012.
41. Australian Institute of Health and Welfare. Estimating the prevalence of osteoporosis in Australia. Canberra: AIHW; 2014.
42. Nguyen TV, Center JR, Eisman JA. Osteoporosis: Underrated, underdiagnosed and undertreated. Med J Aust. 2004;180(5):S18.
43. Harrington JT, Broy SB, Derosa AM, Licata AA, Shewmon DA. Hip fracture patients are not treated for osteoporosis: A call to action. Arthritis Care Res (Hoboken). 2002;47(6):651-4.
44. Kanis JA, Gluer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. Osteoporos Int. 2000;11(3):192-202.
45. Henry YM, Fatayerji D, Eastell R. Attainment of peak bone mass at the lumbar spine, femoral neck and radius in men and women: relative contributions of bone size and volumetric bone mineral density. Osteoporos Int. 2004;15(4):263-73.
46. Kanis JA. Assessment of osteoporosis at the primary health-care level. UK: University of Sheffield, 2007.
47. Kanis JA, Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report. Osteoporos Int. 1994;4(6):368-81.
48. Liu G, Peacock M, Eilam O, Dorulla G, Braunstein E, Johnston CC. Effect of osteoarthritis in the lumbar spine and hip on bone mineral density and diagnosis of osteoporosis in elderly men and women. Osteoporos Int. 1997;7(6):564-9.
49. Ewald D. Osteoporosis prevention and detection in general practice. Aust Fam Physician. 2012;41:104-8.
50. Kanis JA, Johnell O, Odén A, Johansson H, McCloskey E. FRAX® and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385-97.
51. Diseases WHOCCfMB. FRAX®: WHO fracture risk assessment tool 2015 [cited 2015 8th June]. Available from: https://www.shef.ac.uk/FRAX/tool.aspx?country=31.

52. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int. 2001;12(12):989-95.
53. Kanis JA, McCloskey E, Johansson H, Oden A, Leslie W. FRAX® with and without bone mineral density. Calcif Tissue Int. 2012;90(1):1-13.
54. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. Case finding for the management of osteoporosis with FRAX®—assessment and intervention thresholds for the UK. Osteoporos Int. 2008;19(10):1395-408.
55. Crockett JC, Rogers MJ, Coxon FP, Hocking LJ, Helfrich MH. Bone remodelling at a glance. J Cell Sci. 2011;124(7):991-8.
56. Keller J, Schinke T. The role of the gastrointestinal tract in calcium homeostasis and bone remodeling. Osteoporos Int. 2013;24(11):2737-48.
57. National Center for Biotechnology Information. MeSH database: Health Behavior: U.S. National Library of Medicine; 2015 [cited 2015 16 March]. Available from: http://www.ncbi.nlm.nih.gov/mesh/?term=health+behaviour.
58. Poole KES, Compston JE. Osteoporosis and its management. BMJ. 2006;333(7581):1251-6.
59. DeLuca HF. Overview of general physiologic features and functions of vitamin D. The American Journal of Clinical Nutrition. 2004;80(6):1689S-96S.
60. Johnston CC, Miller JZ, Slemenda CW, Reister TK, Hui S, Christian JC, et al. Calcium supplementation and increases in bone mineral density in children. N Engl J Med. 1992;327(2):82-7.
61. Halioua L, Anderson JJ. Lifetime calcium intake and physical activity habits: independent and combined effects on the radial bone of healthy premenopausal Caucasian women. The American Journal of Clinical Nutrition. 1989;49(3):534-41.
62. Flynn A. The role of dietary calcium in bone health. Proc Nutr Soc. 2003;62(04):851-8.
63. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. The American Journal of Clinical Nutrition. 2004;80(4):1066-74.
64. Nguyen TV, Center JR, Eisman JA. Osteoporosis in elderly men and women: Effects of dietary calcium, physical activity, and body mass index. J Bone Miner Res. 2000;15(2):322-31.

65. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: A meta-analysis. Lancet. 2007;370(9588):657-66.
66. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr. 2007;86(6):1780-90.
67. Kristal AR, Peters U, Potter JD. Is it time to abandon the food frequency questionnaire? Cancer Epidem Biomar. 2005;14(12):2826-8.
68. Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, LaCroix AZ, Anderson GL, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int. 2013;24(2):567-80.
69. Ebeling PR, Daly RM, Kerr DA, Kimlin MG. Building healthy bones throughout life: an evidence-informed strategy to prevent osteoporosis in Australia. Med J Aust. 2013;199(7 Suppl):S1.
70. Christianson MS, Shen W. Osteoporosis prevention and management: nonpharmacologic and lifestyle options. Clin Obstet Gynecol. 2013;56(4):703-10.
71. Drake MT, Murad MH, Mauck KF, Lane MA, Undavalli C, Elraiyah T, et al. Risk factors for low bone mass-related fractures in men: A systematic review and meta-analysis. J Clin Endocr Metab. 2012;97(6):1861-70.
72. Papaioannou A, Kennedy CC, Cranney A, Hawker G, Brown JP, Kaiser SM, et al. Risk factors for low BMD in healthy men age 50 years or older: a systematic review. Osteoporos Int. 2009;20(4):507-18.
73. Knoke JD, Barrett-Connor E. Weight loss: a determinant of hip bone loss in older men and women. The Rancho Bernardo Study. Am J Epidemiol. 2003;158(12):1132-8.
74. Hannan MT, Felson DT, Dawson-Hughes B, Tucker KL, Cupples LA, Wilson PWF, et al. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res. 2000;15(4):710-20.
75. Lassemillante A-CM, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors II: A meta-analysis of men not on androgen deprivation therapy. Endocrine. 2015.
76. Lassemillante A-CM, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors: A meta-analysis. Endocrine. 2014;45(3):370-81.

77. Pradhan MR, Mandhani A, Chipde SS, Srivastava A, Singh M, Kapoor R. Bone densitometric assessment and management of fracture risk in Indian men of prostate cancer on androgen deprivation therapy: Does practice pattern match the guidelines? Indian J Urol. 2012;28(4):399-404.
78. Nadler M, Alibhai S, Catton P, Catton C, To MJ, Jones JM. Osteoporosis knowledge, health beliefs, and healthy bone behaviours in patients on androgen-deprivation therapy (ADT) for prostate cancer. BJU Int. 2013:n/a-n/a.
79. Rosenstock IM. Why people use health services. The Milbank Memorial Fund quarterly. 1966;44(3):Suppl:94-127.
80. Rosenstock IM, Strecher VJ, Becker MH. Social Learning Theory and the Health Belief Model. Health Educ Behav. 1988;15(2):175-83.
81. Glanz K, Rimer BK, Viswanath K. Health behavior and health education : Theory, research, and practice. Hoboken: Wiley; 2008. Available from: http://UQL.eblib.com.au/patron/FullRecord.aspx?p=353367.
82. Janz NK, Becker MH. The Health Belief Model: A decade later. Health Educ Behav. 1984;11(1):1-47.
83. McLeod KM, Johnson CS. A systematic review of osteoporosis health beliefs in adult men and women. Journal of Osteoporosis. 2011;2011.
84. Bandura A. Self-efficacy : The exercise of control. New York: W.H. Freeman; 1997. 604 p.
85. Horan ML, Kim KK, Gendler P, Froman RD, Patel MD. Development and evaluation of the osteoporosis self-efficacy scale. Res Nurs Health. 1998;21(5):395-403.
86. Werner P. Knowledge about osteoporosis: Assessment, correlates and outcomes. Osteoporos Int. 2005;16(2):115-27.
87. Renpenning KM, Taylor SG, Ebooks C. Self-care science, nursing theory, and evidence-based practice. New York: Springer Pub; 2011.
88. Orem DE. Nursing : Concepts of practice. 4th ed. ed. St. Louis,: Mosby Year Book; 1991. 385 p.
89. Kennedy AP, Rogers AE. Improving patient involvement in chronic disease management: The views of patients, GPs and specialists on a guidebook for ulcerative colitis. Patient Educ Couns. 2002;47(3):257-63.
90. Sheikh I, Ogden J. The role of knowledge and beliefs in help seeking behaviour for cancer: A quantitative and qualitative approach. Patient Educ Couns. 1998;35(1):35-42.
91. Rizzoli R, Abraham C, Brandi M-L. Nutrition and bone health: turning knowledge and beliefs into healthy behaviour. Curr Med Res Opin. 2014;30(1):131-41.

92. Harrison JA, Mullen PD, Green LW. A meta-analysis of studies of the Health Belief Model with adults. Health Educ Res. 1992;7(1):107-16.
93. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU Guidelines on Prostate Cancer. EAU, 2013.
94. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and treatment. In: National Institute for Health and Care Excellence (NICE). London (UK) 2014.
95. Cancer Council Australia Advanced Prostate Cancer Guidelines Working Party. Management of locally and advanced prostate cancer Sydney: Cancer Council Australia; 2010 [cited 2015 17 March]. Available from: http://wiki.cancer.org.au/australia/Guidelines:Prostate_cancer/Management/Locally_advanced_and_metastatic.
96. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: The Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporos Int. 1994;4(5):277-82.
97. Nguyen T, Sambrook P, Kelly P, Jones G, Lord S, Freund J, et al. Prediction of osteoporotic fractures by postural instability and bone density. Br Med J. 1993;307(6912):1111-5.
98. Angus RM, Sambrook PN, Pocock NA, Eisman JA. A simple method for assessing calcium intake in Caucasian women. J Am Diet Assoc. 1989;89(2):209-14.
99. Raab CA, Gregerson D, Shaw JM, Snow C. Postmenopausal women take steps to reduce their osteoporosis risk. Womens Health Issues. 1999;9(4):211-8.
100. Curry LC, Hogstel MO, Davis GC, Frable PJ. Population-based osteoporosis education for older women. Public Health Nurs. 2002;19(6):460-9.
101. Chang SF. Explore the effectors of bone mineral density in community women. J Nurs Res. 2004;12(4):327-36.
102. Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. How many women have osteoporosis? J Bone Miner Res. 2005;20(5):886-92.
103. Sutton A, Dian L, Guy P. Osteoporosis in men: an underrecognized and undertreated problem. B C Med J. 2011;53(10):535-40.
104. Deng JH, Yang LP, Wang LS, Zhou DF. Effect of androgen deprivation therapy on bone mineral density in prostate cancer patients. Asian J Androl. 2004;6(1):75-7.
105. Bernat MM, Pasini J, Marekovic Z. Changes in bone mineral density in patients with prostate cancer treated with androgen deprivation therapy. Coll Antropol. 2005;29(2):589-91.

106. Peters JL, Fairney A, Kyd P, Patel A, Rogers S, Webster JJ, et al. Bone loss associated with the use of LHRH agonists in prostate cancer. Prostate Cancer Prostatic Dis. 2001;4(3):161-6.
107. Wang W, Yuasa T, Tsuchiya N, Maita S, Kumazawa T, Inoue T, et al. Bone mineral density in Japanese prostate cancer patients under androgen-deprivation therapy. Endocrine related cancer. 2008;15(4):943-52.
108. Conde FA, Sarna L, Oka RK, Vredevoe DL, Rettig MB, Aronson WJ. Age, body mass index, and serum prostate-specific antigen correlate with bone loss in men with prostate cancer not receiving androgen deprivation therapy. Urology. 2004;64(2):335-40.
109. Berruti A, Dogliotti L, Terrone C, Cerutti S, Isaia G, Tarabuzzi R, et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J Urol. 2002;167(6):2361-7; discussion 7.
110. Smith MR, McGovern FJ, Fallon MA, Schoenfeld D, Kantoff PW, Finkelstein JS. Low bone mineral density in hormone-naive men with prostate carcinoma. Cancer. 2001;91(12):2238-45.
111. Genant HK, Grampp S, Gluer CC, Faulkner KG, Jergas M, Engelke K, et al. Universal standardization for dual x-ray absorptiometry: Patient and phantom cross-calibration results. J Bone Miner Res. 1994;9(10):1503-14.
112. Fan B, Lu Y, Genant H, Fuerst T, Shepherd J. Does standardized BMD still remove differences between Hologic and GE-Lunar state-of-the-art DXA systems? Osteoporos Int. 2010;21(7):1227-36.
113. Cauley JA, Fullman RL, Stone KL, Zmuda JM, Bauer DC, Barrett-Connor E, et al. Factors associated with the lumbar spine and proximal femur bone mineral density in older men. Osteoporosis Int. 2005;16(12):1525-37.
114. Dai LY. The relationship between osteoarthritis and osteoporosis in the spine. Clin Rheumatol. 1998;17(1):44-6.
115. Bubendorf L, Schopfer A, Wagner U, Sauter G, Moch H, Willi N, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol. 2000;31(5):578-83.
116. Keller ET, Brown J. Prostate cancer bone metastases promote both osteolytic and osteoblastic activity. J Cell Biochem. 2004;91(4):718-29.
117. Batson OV. The function of the vertebral veins and their role in the spread of metastases. Ann Surg. 1940;112(1):138-49.

118. Buijs JT, van der Pluijm G. Osteotropic cancers: From primary tumor to bone. Cancer Lett. 2009;273(2):177-93.
119. Arya M, Bott SR, Shergill IS, Ahmed HU, Williamson M, Patel HR. The metastatic cascade in prostate cancer. Surg Oncol. 2006;15(3):117-28.
120. Bruder JM, Ma JZ, Basler JW, Welch MD. Prevalence of osteopenia and osteoporosis by central and peripheral bone mineral density in men with prostate cancer during androgen-deprivation therapy. Urology. 2006;67(1):152-5.
121. Chen Z, Maricic M, Nguyen P, Ahmann FR, Bruhn R, Dalkin BL. Low bone density and high percentage of body fat among men who were treated with androgen deprivation therapy for prostate carcinoma. Cancer. 2002;95(10):2136-44.
122. Farhat GN, Taioli E, Cauley JA, Zmuda JM, Orwoll E, Bauer DC, et al. The association of bone mineral density with prostate cancer risk in the osteoporotic fractures in men (MrOS) study. Cancer Epidem Biomar. 2009;18(1):148-54.
123. Panju AH, Breunis H, Cheung AM, Leach M, Fleshner N, Warde P, et al. Management of decreased bone mineral density in men starting androgen-deprivation therapy for prostate cancer. BJU Int. 2009;103(6):753-7.
124. The International Society for Clinical Densitometry. ISCD Official Positions. 2007.
125. World Health Organization. WHO scientific group on the assessement of osteoporosis at primary healthcare level. Geneva: World Health Organization, 2007 Summary meeting report 5-7 May 2004.
126. National comprehensive cancer network. NCCN guidelines for prostate cancer (version 2.2014) 2014 [updated 1st April 2014; cited 2014 14th APril]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
127. Yuasa T, Maita S, Tsuchiya N, Takahashi S, Hatake K, Fukui I, et al. Relationship between bone mineral density and androgen-deprivation therapy in Japanese prostate cancer patients. J Urol. 2010;183(4):e335.
128. Australian Institute of Health and Welfare. Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Cancer series no 69. Canberra: AIHW; 2012.
129. Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al. Prostate cancer mortality at 11 years of follow-up. N Engl J Med. 2012;366(11):981-90.
130. Ruth E, Roman G, Alex T, Elisabeth MW, David FP, Eveline AMH, et al. The prostate cancer conundrum revisited. Cancer. 2012;118(23):5955-63.

131. Niraula S, Le LW, Tannock IF. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: A systematic review of randomized trials. J Clin Oncol. 2013;31(16):2029-36.
132. Schuit SCE, van der Klift M, Weel AEAM, de Laet CEDH, Burger H, Seeman E, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone. 2004;34(1):195-202.
133. Kitson A, Harvey G, McCormack B. Enabling the implementation of evidence based practice: A conceptual framework. Qual Health Care. 1998;7(3):149-58.
134. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: A consensus approach. Qual Saf Health Care. 2005;14(1):26-33.
135. Schwartz GG. Prostate cancer, serum parathyroid hormone, and the progression of skeletal metastases. Cancer Epidem Biomar. 2008;17(3):478-83.
136. Murray R, Grill V, Crinis N, Ho P, Davison J, Pitt P. Hypocalcemic and normocalcemic hyperparathyroidism in patients with advanced prostatic cancer. J Clin Endocr Metab. 2001;86(9):4133-8.
137. Skinner HG, Schwartz GG. The relation of serum parathyroid hormone and serum calcium to serum levels of prostate-specific antigen: A population-based study. Cancer Epidemiology Biomarkers & Prevention. 2009;18(11):2869-73.
138. Ralston SH, de Crombrugghe B. Genetic regulation of bone mass and susceptibility to osteoporosis. Genes Dev. 2006;20(18):2492-506.
139. Nguyen TV, Kelly PJ, Sambrook PN, Gilbert C, Pocock NA, Eisman JA. Lifestyle factors and bone density in the elderly: Implications for osteoporosis prevention. J Bone Miner Res. 1994;9(9):1339-46.
140. Zhumkhawala A-A, Gleason JM, Cheetham TC, Niu F, Loo RK, Dell RM, et al. Osteoporosis management program decreases incidence of hip fracture in patients with prostate cancer receiving androgen deprivation therapy. Urology. 2013;81(5):1010-7.
141. Van Tongeren LS, Duncan GG, Kendler DL, Pai H. Implementation of osteoporosis screening guidelines in prostate cancer patients on androgen ablation. J Clin Densitom. 2009;12(3):287-91.
142. Israeli RS. Managing bone loss and bone metastases in prostate cancer patients: A focus on bisphosphonate therapy. Reviews in Urology. 2008;10(2):99-110.
143. Lisspers J, Sundin O, Ohman A, Hofman-Bang C, Ryden L, Nygren A. Long-term effects of lifestyle behavior change in coronary artery disease: effects on recurrent

coronary events after percutaneous coronary intervention. Health Psychol. 2005;24(1):41-8.
144. National Health and Medical Research Council. Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men. NHMRC: The Royal Australian College of General Practitioners; 2010.
145. Wallace T, Weaver C, Alexander D, Boushey C, Dawson-Hughes B, Lappe J, et al. Calcium plus vitamin D supplementation and risk of fractures: An updated meta-analysis from NOF. The FASEB J. 2015;29(1 Supplement).
146. Alibhai SM, Rahman S, Warde PR, Jewett MA, Jaffer T, Cheung AM. Prevention and management of osteoporosis in men receiving androgen deprivation therapy: A survey of urologists and radiation oncologists. Urology. 2006;68(1):126-31.
147. Gaines JM, Marx KA. Older men's knowledge about osteoporosis and educational interventions to increase osteoporosis knowledge in older men: A systematic review. Maturitas. 2011;68(1):5-12.
148. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. Implement Sci. 2012;7:50.
149. Plawecki K, Chapman-Novakofski K. Effectiveness of community intervention in improving bone health behaviors in older adults. J Nutr Gerontol Geriatr. 2013;32(2):145-60.
150. Nadler M, Alibhai S, Catton P, Catton C, Jones J. The impact of bone mineral density testing, fracture assessment, and osteoporosis education in men treated by androgen deprivation for prostate cancer: A pilot study. Support Care Cancer. 2014;22(9):2409-15.
151. Nielsen D, Ryg J, Nissen N, Nielsen W, Knold B, Brixen K. Multidisciplinary patient education in groups increases knowledge on osteoporosis: A randomized controlled trial. Scand J Public Healt. 2008;36(4):346-52.
152. Tussing L, Chapman-Novakofski K. Osteoporosis prevention education: Behavior theories and calcium intake. J Am Diet Assoc. 2005;105(1):92-7.
153. Spahn JM, Reeves RS, Keim KS, Laquatra I, Kellogg M, Jortberg B, et al. State of the evidence regarding behavior change theories and strategies in nutrition counseling to facilitate health and food behavior change. J Am Diet Assoc. 2010;110(6):879-91.
154. Bishop FL, Rea A, Lewith H, Chan YK, Saville J, Prescott P, et al. Complementary medicine use by men with prostate cancer: A systematic review of prevalence studies. Prostate Cancer Prostatic Dis. 2011;14(1):1-13.

155. Academy of Nutrition and Dietetics. Nutrition Terminology Reference Manual (eNCPT): Dietetics Language for Nutrition Care 2014 [updated 2014; cited 2015 4 March]. Available from: https://ncpt.webauthor.com.
156. Academy of Nutrition and Dietetics. Nutrition Terminology Reference Manual (eNCPT): Dietetics Language for Nutrition Care [Theoretical Basis/Approach (C - 1) - Health Belief Model] 2014 [cited 2015 3 March]. Available from: https://ncpt.webauthor.com/pubs/idnt-en/codeC-1-HBM.
157. Datta M, Schwartz GG. Calcium and vitamin D supplementation during androgen deprivation therapy for prostate cancer: A critical review. The Oncologist. 2012;17(9):1171-9.
158. Brecher LS, Pomerantz SC, Snyder BA, Janora DM, Klotzbach-Shimomura KM, Cavalieri TA. Osteoporosis prevention project: a model multidisciplinary educational intervention. J Am Osteopath Assoc. 2002;102(6):327-35.
159. Nielsen D, Ryg J, Nielsen W, Knold B, Nissen N, Brixen K. Patient education in groups increases knowledge of osteoporosis and adherence to treatment: A two-year randomized controlled trial. Patient Educ Couns.81(2):155-60.
160. Davison BJ, Wiens K, Cushing M. Promoting calcium and vitamin D intake to reduce the risk of osteoporosis in men on androgen deprivation therapy for recurrent prostate cancer. Support Care Cancer. 2012;20(10):2287-94.

APPENDIX I Medicare pharmaceutical benefits scheme claims for Androgen Deprivation Therapy (2003 to 2015)

Table A 1 Medicare Pharmaceutical Benefits Scheme claims for ADT for the financial years from 2003 to 2015.

	Gosereline and bicalutamide	Leuprorelin	Degarelix	Total
2003/04	0	205	0	205
2004/05	0	2493	0	2493
2005/06	0	4740	0	4740
2006/07	111	29044	0	29155
2007/08	1762	32755	0	34517
2008/09	2885	35523	0	38408
2009/10	3556	35544	0	39100
2010/11	4369	34723	0	39092
2011/12	4824	35465	0	40289
2012/13	5280	34790	0	40070
2013/14	5491	36107	1751	43349
YTD 2014/2015	2852	18707	3915	25474
Total	31130	300096	5666	336892

YTD; year to date; Medicare Pharmaceutical Benefits Scheme item number for Gosereline and bicalutamide 9064C, 9066E, 9065D; Medicare Pharmaceutical Benefits Scheme item number for Leuprorelin 8875D, 8859G, 8877F, 8709J, 8707G, 8708H, 8876E; Medicare Pharmaceutical Benefits Scheme item number for Degarelix 2785N, 2784M.

APPENDIX II FRAX® algorithm

Figure A 1 Example of the FRAX algorithm, specific to Australia.

Sourced from (51).

APPENDIX III Literature search strategy for meta-analyses of osteoporosis in men with prostate cancer

Database: PUBMED

Osteoporosis[Mesh] OR osteoporosis OR Osteoporoses OR “Osteoporosis, Post-Traumatic” OR “Osteoporosis, Post Traumatic” OR “Post-Traumatic Osteoporoses” OR “Post-Traumatic Osteoporosis” OR “Osteoporosis, Senile” OR “Osteoporoses, Senile” OR “Senile Osteoporoses” OR “Senile Osteoporosis” OR “Osteoporosis, Age-Related” OR “Osteoporosis, Age Related” OR “Bone Loss, Age-Related” OR “Age-Related Bone Loss” OR “Age-Related Bone Losses” OR “Bone Loss, Age Related” OR “Bone Losses, Age-Related” OR “Age-Related Osteoporosis” OR “Age Related Osteoporosis” OR “Age-Related Osteoporoses” OR “Osteoporoses, Age-Related”

AND

"Prostatic Neoplasms"[Mesh] OR “Prostate Neoplasms” OR “Prostate Neoplasm” OR “Prostatic Neoplasm” OR “Prostate Cancer” OR “Prostate Cancers” OR “Cancer of the Prostate” OR “Prostatic Cancer” OR “Cancer of Prostate” OR “prostate tumor” OR “prostate tumors” OR “prostate tumour” OR “prostate tumours” OR “prostate carcinoma” OR “prostate carcinomas” OR “prostatic carcinoma” OR “prostatic carcinomas” OR “carcinoma of the prostate” OR “carcinoma of prostate”

Database: EMBASE

‘OSTEOPOROSIS’/EXP OR osteoporosis OR osteoporoses OR 'osteoporosis, post-traumatic' OR 'osteoporosis, post traumatic' OR 'post-traumatic osteoporoses' OR 'post-traumatic osteoporosis' OR 'osteoporosis, senile' OR 'osteoporoses, senile' OR 'senile osteoporoses' OR 'senile osteoporosis' OR 'osteoporosis, age-related' OR 'osteoporosis, age related' OR 'bone loss, age-related' OR 'age-related bone loss' OR 'age-related bone losses' OR 'bone loss, age related' OR 'bone losses, age-related' OR 'age-related osteoporosis' OR 'age related osteoporosis' OR 'age-related osteoporoses' OR 'osteoporoses, age-related'

AND

‘Prostate cancer’/exp OR “Prostate Neoplasms” OR “Prostate Neoplasm” OR “Prostatic Neoplasm” OR “Prostate Cancer” OR “Prostate Cancers” OR “Cancer of the Prostate” OR “Prostatic Cancer” OR “Cancer of Prostate” OR “prostate tumor” OR “prostate tumors” OR “prostate tumour” OR “prostate tumours” OR “prostate carcinoma” OR “prostate

carcinomas” OR “prostatic carcinoma” OR “prostatic carcinomas” OR “carcinoma of the prostate” OR “carcinoma of prostate”

APPENDIX IV Facts On Osteoporosis Quiz (FOOQ) with Men's Osteoporosis Knowledge Questionnaire (MOKQ)

Facts on Osteoporosis Quiz

Osteoporosis refers to weakened bone strength. It is commonly called "brittle bones" because this disease increases the risk of bone fractures.

Completely fill in the circle of the appropriate answer.

	True	False	Don't Know
1. Physical activity increases the risk of osteoporosis.	Ⓣ	Ⓕ	Ⓓ
2. High impact exercise (weight training) improves bone health.	Ⓣ	Ⓕ	Ⓓ
3. Most people gain bone mass after 30 years of age.	Ⓣ	Ⓕ	Ⓓ
4. Low-weight women have osteoporosis more than heavy women.	Ⓣ	Ⓕ	Ⓓ
5. Alcoholism is not linked to the occurrence of osteoporosis.	Ⓣ	Ⓕ	Ⓓ
6. The most important time to build bone strength is between 9 and 17 years of age.	Ⓣ	Ⓕ	Ⓓ
7. Normally, bone loss speeds up after menopause.	Ⓣ	Ⓕ	Ⓓ
8. High caffeine combined with low calcium intake increases the risk of osteoporosis.	Ⓣ	Ⓕ	Ⓓ
9. There are many ways to prevent osteoporosis.	Ⓣ	Ⓕ	Ⓓ
10. Without preventative measures 20% of women older than 50 years will have a fracture due to osteoporosis in their lifetime.	Ⓣ	Ⓕ	Ⓓ
11. There are treatments for osteoporosis after it develops.	Ⓣ	Ⓕ	Ⓓ
12. A lifetime of low intake of calcium and vitamin D does not increase the risk of osteoporosis.	Ⓣ	Ⓕ	Ⓓ
13. Smoking does not increase the risk of osteoporosis.	Ⓣ	Ⓕ	Ⓓ
14. Walking has a great effect on bone health.	Ⓣ	Ⓕ	Ⓓ

	True	False	Don't Know
15. After menopause, women not on estrogen need about 1500mg of calcium (for example, 5 glasses of milk) daily.	Ⓣ	Ⓕ	Ⓓ
16. Osteoporosis affects men and women.	Ⓣ	Ⓕ	Ⓓ
17. Early menopause is not a risk factor for osteoporosis.	Ⓣ	Ⓕ	Ⓓ
18. Replacing hormones after menopause cannot slow down bone loss.	Ⓣ	Ⓕ	Ⓓ
19. Children 9 to 17 years of age get enough calcium from one glass of milk each day to prevent osteoporosis.	Ⓣ	Ⓕ	Ⓓ
20. Family history of osteoporosis is not a risk factor for osteoporosis.	Ⓣ	Ⓕ	Ⓓ

Men's Osteoporosis Knowledge Questionnaire

	True	False	Don't Know
21. Small frame/low weight men have osteoporosis more than larger framed/heavier men.	Ⓣ	Ⓕ	Ⓓ
22. Bone loss increases in men after the age of 70 years.	Ⓣ	Ⓕ	Ⓓ
23. Without preventative measures 25% of men older than 50 years will have a fracture because of osteoporosis in their lifetime.	Ⓣ	Ⓕ	Ⓓ
24. After the age of 50 years, men need about 1,200mg of calcium daily.	Ⓣ	Ⓕ	Ⓓ
25. Low testosterone levels are not a risk factor for osteoporosis.	Ⓣ	Ⓕ	Ⓓ
26. Hormone treatment for prostate cancer decreases the risk of osteoporosis.	Ⓣ	Ⓕ	Ⓓ

APPENDIX V Osteoporosis Self-Efficacy Scale

Osteoporosis Self-Efficacy Scale
We are interested in learning how confident you feel about doing the following activities. Everyone has different experiences which will make each person more or less confident in doing the following things. Thus, there are no right or wrong answers to this questionnaire. It is your opinion that is important. In this questionnaire, EXERCISE means activities such as walking, swimming, golfing, biking, aerobic dancing.

Place your "X" anywhere on the answer line that you feel best describes your confidence level.

If it were recommended that you do any of the following THIS WEEK, how confident or certain would you be that you could:

Begin a new or different exercise program

Not at all confident _____ Very confident

Change your exercise habits

Not at all confident _____ Very confident

Put forth the effort required to exercise

Not at all confident _____ Very confident

Do exercises even if they are difficult

Not at all confident _____ Very confident

Maintain a regular exercise program

Not at all confident _____ Very confident

Exercise for the appropriate length of time

Not at all confident _____ Very confident

Do exercises even if they are tiring

Not at all confident _____ Very confident

Stick to your exercise program

Not at all confident _____ Very confident

Exercise at least 3 times a week

Not at all confident _____ Very confident

Do the type of exercise that you are supposed to do

Not at all confident _____ Very confident

Begin to eat more calcium rich foods

Not at all confident _____ Very confident

Increase your calcium intake

Not at all confident _____ Very confident

Consume adequate amount of calcium rich foods

Not at all confident _____ Very confident

Eat calcium rich foods on a regular basis

Not at all confident _____ Very confident

Change your diet to include more calcium rich foods

Not at all confident _____ Very confident

Eat calcium rich foods as often as you are supposed to do

Not at all confident _____ Very confident

Select appropriate foods to increase your calcium intake

Not at all confident _____ Very confident

Stick to a diet which gives an adequate amount of calcium

Not at all confident _____ Very confident

Obtain foods that give an adequate amount of calcium

Not at all confident _____ Very confident

Remember to eat calcium rich foods

Not at all confident _____ Very confident

Take calcium supplements if you don't get enough calcium from your diet

Not at all confident _____ Very confident

APPENDIX VI Osteoporosis Health Belief Scale

Osteoporosis Health Belief Scale

(Interviewer: Read the following instructions *slowly*)

Osteoporosis is a condition in which the bones become excessively thin (porous) and weak so that they are fracture prone (they break easily).

I am going to ask you some questions about your beliefs about osteoporosis. There are no right or wrong answers. Everyone has different experiences which will influence how they feel. After I read each statement, tell me if you STRONGLY DISAGREE, DISAGREE, are NEUTRAL, AGREE, or STRONGLY AGREE with each statement.

It is important that you answer according to your actual beliefs and not according to how you feel you should believe or how you think we want you to believe. We need the answers that best explain how you feel.

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1. Your chances of getting osteoporosis are high.	❍	❍	❍	❍	❍
2. Because of your body build, you are more likely to develop osteoporosis.	❍	❍	❍	❍	❍
3. It is extremely likely that you will get osteoporosis.	❍	❍	❍	❍	❍
4. There is a good chance that you will get osteoporosis.	❍	❍	❍	❍	❍
5. You are more likely than the average person to get osteoporosis.	❍	❍	❍	❍	❍
6. Your family history makes it more likely that you will get osteoporosis.	❍	❍	❍	❍	❍
7. The thought of having osteoporosis scares you.	❍	❍	❍	❍	❍
8. If you had osteoporosis you would be crippled.	❍	❍	❍	❍	❍
9. Your feelings about yourself would change if you got osteoporosis.	❍	❍	❍	❍	❍
10. It would be very costly if you got					

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
osteoporosis.	❍	❍	❍	❍	❍
11. When you think about osteoporosis you get depressed.	❍	❍	❍	❍	❍
12. It would be very serious if you got osteoporosis.	❍	❍	❍	❍	❍
13. Regular exercise prevents problems that would happen from osteoporosis.	❍	❍	❍	❍	❍
14. You feel better when you exercise to prevent osteoporosis.	❍	❍	❍	❍	❍
15. Regular exercise helps to build strong bones.	❍	❍	❍	❍	❍
16. Exercising to prevent osteoporosis also improves the way your body looks.	❍	❍	❍	❍	❍
17. Regular exercise cuts down the chances of broken bones.	❍	❍	❍	❍	❍
18. You feel good about yourself when you exercise to prevent osteoporosis.	❍	❍	❍	❍	❍
For the following questions, when I say "taking in enough calcium" it means taking enough calcium by eating calcium rich foods and/or taking calcium supplements.					
19. Taking in <u>enough calcium</u> prevents problems from osteoporosis.	❍	❍	❍	❍	❍
20. You have lots to gain from taking in <u>enough calcium</u> to prevent osteoporosis.	❍	❍	❍	❍	❍
21. Taking in <u>enough calcium</u> prevents painful osteoporosis.	❍	❍	❍	❍	❍
22. You would not worry as much about osteoporosis if you took in <u>enough calcium</u>.	❍	❍	❍	❍	❍
23. Taking in <u>enough calcium</u> cuts down on your chances of broken bones.	❍	❍	❍	❍	❍
24. You feel good about yourself when you take in <u>enough calcium</u> to prevent osteoporosis.	❍	❍	❍	❍	❍
25. You feel like you are not strong enough to exercise regularly.	❍	❍	❍	❍	❍
26. You have no place where you can exercise.	❍	❍	❍	❍	❍

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
27. Your spouse or family discourages you from exercising.	❍	❍	❍	❍	❍
28. Exercising regularly would mean starting a new habit which is hard for you to do.	❍	❍	❍	❍	❍
29. Exercising regularly makes you uncomfortable.	❍	❍	❍	❍	❍
30. Exercising regularly upsets your every day routine.	❍	❍	❍	❍	❍
31. Calcium rich foods cost too much.	❍	❍	❍	❍	❍
32. Calcium rich foods do not agree with you.	❍	❍	❍	❍	❍
33. You do not like calcium rich foods.	❍	❍	❍	❍	❍
34. Eating calcium rich foods means changing your diet which is hard to do.	❍	❍	❍	❍	❍
35. In order to eat more calcium rich foods you have to give up other foods that you like.	❍	❍	❍	❍	❍
36. Calcium rich foods have too much cholesterol.	❍	❍	❍	❍	❍
37. You eat a well-balanced diet.	❍	❍	❍	❍	❍
38. You look for new information related to health.	❍	❍	❍	❍	❍
39. Keeping healthy is very important for you.	❍	❍	❍	❍	❍
40. You try to discover health problems early.	❍	❍	❍	❍	❍
41. You have a regular health check-up even when you are not sick.	❍	❍	❍	❍	❍
42. You follow recommendations to keep you healthy.	❍	❍	❍	❍	❍

Date: Participant Name.: Participant Initials:

APPENDIX VII Diet History Form

Instructions:

- Think about what you usually eat on a weekly basis.
- Please note down these foods and drinks with as much detail as possible, inclu. type of food (eg toast with jam), amount of food (use cups, teaspoon, tablespoon measures where possible), and how often the food is consumed (eg frequency - 3 out of 7 days in a wk).
- Count any snacks or meals eaten at least an hour apart as separate eating occasions.
- To give you an idea of how to fill this booklet in, please see the sample.
- *Key – Tb = Tablespoon; tsp = teaspoon; sl = slice.*

Sample of how to fill in the diet history:

Prompts	Type and amount	Frequency
Breakfast	**2 sl toast - wholemeal** **1 Tb margarine** **2 Tb jam** **1 cup coffee with 20mL full cream milk and 1 tsp sugar** **2 rashers bacon cooked in 1 Tb olive oil** **1 boiled egg** **½ tomato cooked in 1 tsp olive oil** **1 slice (sl) toast**	**5 days out of 7 (or 5/7)** **5/7** **2 days out of 7 (or 2/7)** **2/7**

Part 0: Anything consumed before breakfast (please note any differences for weekends)

How many times a week do you eat something **before** breakfast? _____ What time do you usually do this?_____

Prompts	Tick	Type and amount	Frequency
Tea / Coffee Milk Sugar Toast Biscuit Other			

Date: Participant Name.: Participant Initials:

Part 1: Breakfast (please note any differences for weekends)

How many times a week do you eat breakfast? _____ What time do you usually eat breakfast? _____

Prompts	Tick	Type and amount	Frequency
Breakfast cereal Muesli / Oats Cereal bars			
Bread / Toast spreads eg margarine, butter, jam etc.			
Muffins Crumpets Croissants Pancakes			
Yoghurt Fruit Salad			
Protein shakes/powders			
Eggs (boiled scrambled, fried, poached,) Bacon Baked beans Sausages Hash browns Sauce/s Oil / Fat Other			

Drinks: Tea, coffee, juice and others (hot chocolate, fruit juice, smoothie, alcohol) with sugar/sweetener

Type & amount: _____Frequency:_____

Type & amount: _____Frequency:_____

Type & amount: _____Frequency:_____

Date: Participant Name.: Participant Initials:

Part 2: Morning Tea (please note any differences for weekends)

How many times a week do you eat morning tea? _____ What time do you usually eat morning tea? _____

Prompts	Tick	Type and Amount	Frequency
Tea Coffee Sugar / Sweetener Milk Juice Flavoured milk Alcohol Smoothie Hot Chocolate			
Yoghurt Fruit			
Cereal bars Biscuits Cake Muffins Chocolate Other			

Date: Participant Name.: Participant Initials:

Part 3: Lunch (please note any differences for weekends)

How many times a week do you eat lunch? _____ What time do you usually eat lunch? _____

Prompts	Tick	Type and amount	Frequency
Sandwich bread fillings eg - salad, meat cheese spreads eg – jam, margarine sauces eg – tomato, mustard, mayonnaise Salads dressing ingredients Soups Hot Meals eg spaghetti Bolognese, pasta Takeaway foods pizzas pies hamburgers hot chips Other		*****SALT*****	

Drinks: Tea, coffee, juice, soft drink, cordial, alcohol etc

Type & amount: _____ Frequency: _____

Type & amount: _____ Frequency: _____

Date: Participant Name.: Participant Initials:

Part 4: Afternoon Tea (please note any differences for weekends)

How many times a week do you eat afternoon tea? _____ What time do you usually eat afternoon tea? _____

Prompts	Tick	Type and amount	Frequency
Tea			
Coffee			
Sugar / Sweetener			
Milk			
Juice			
Flavoured milk			
Alcohol			
Smoothie			
Hot Chocolate			
Yoghurt			
Fruit			
Biscuits			
Cake			
Cereal bars			
Muffins			
Chocolate			
Other			

Date: Participant Name.: Participant Initials:

Part 5: Dinner (please note any differences for weekends)

How many times a week do you eat dinner? _____ What time do you usually eat dinner? _____

Prompts	Tick	Type and amount & cooking method	Frequency
Meat – grilled, roasted, crumbed, fried Chicken Fish Pasta Spaghetti Bol Lasagne Stir fries Casseroles Stews Soups Quiche Accompaniments Potato Vegetables Mash Wedges Rice Cous cous Salads Potato chips Gravies Sauce/s		***SALT***	

Drinks: Tea, coffee, alcohol, juice, soft drink, cordial, etc

Type: _____ Frequency:_____

Type: _____ Frequency:_____

Date: Participant Name.: Participant Initials:

Desserts eaten directly after dinner

How many times a week do you eat dessert? _____ What time do you usually eat this? _____

Prompts	Tick	Type & amount	Frequency
Ice cream Fruit Pies Crumbles Cake Pudding Lamingtons Cookies Biscuits			

Date: Participant Name.: Participant Initials:

Part 6: Takeaway/Restaurant Meals/ Eating Out (please note any differences for weekends)

How many times a week do you eat takeaway? _____ What time do you usually eat this? _____

Prompts	Tick	Type and amount	Frequency
McDonald's burger fries shake/drink Kentucky Fried Chicken fried chicken nuggets fries/chips Pizza pan thin-based toppings soft drink Asian food Chinese Japanese Thai Vietnamese Fish and chips battered or fried grilled potato scallops fries/chips Other soft drink Indian food Italian food Mexican food		***SALT***	

Date: Participant Name.: Participant Initials:

Part 7: Evening Snack Foods (please note any differences for weekends)

How many times a week do you eat an evening snack? _____ What time do you usually eat this?_____

Prompts	Tick	Type and amount	Frequency
Tea Coffee Sugar/ Sweetener Milk Juice Flavoured milk Smoothie Alcohol Yoghurt Fruit Biscuits Cake Cereal bars Muffins Chocolate Desserts *mentioned above but eaten at least an hour after dinner.*			

Date: Participant Name.: Participant Initials:

Part 8: Food frequency checklist (only tick if accounted for)

Type of food	Serving size	Frequency
Milk (brand and fat %)		
Flavoured milk (Milo…)		
Fruit		
Fruit Juice		
Soft drinks/cordials/sports drinks		
Alcohol		
Yoghurt		
Cheese		
Ice creams		
Crispbreads/crackers		
Biscuits		
Cakes/scones		
Chocolate		
Chips		
Lollies		
Coffee/Lattés		
Cream		
Eggs		
Fish (type)		
Nuts (almonds, brazil nuts …)		
Tofu		
Beans/Pulses/Legumes		
Canned fish (with or without bones)		

Date: Participant Name.: Participant Initials:

Part 9: Food Preparation Practices

9.1 Butter/Margarine **How much would you have in a day or a week?**_____

What type do you usually use? (please circle)

a) Butter
b) Dairy Blend – regular fat
c) Dairy Blend – reduced fat
d) margarine – regular fat
e) margarine – reduced fat

9.2 Oil/Fat in Cooking **How much would you have in a day or a week?**_____

What type of oil/fat do you use in cooking? (please circle all that you use)

a) Butter
b) Dairy blend
c) Margarine
d) Lard or dripping
e) Olive oil
f) Canola oil
g) Other vegetable oil _____

9.3 Fat on Meats/Chicken **How much would you have in a day or a week?**_____

How much fat is trimmed from meat before cooking/eating? (please circle)

a) None
b) 25%
c) 50%
d) 75%
e) All
f) Other, please specify:_____

How much skin do you eat on chicken? (please circle)

a) None
b) 25%
c) 50%
d) 75%
e) All
f) Other, please specify:_____

Appendix VIII Examples of food groups (major, sub-major, and minor) used in the Australian Health Survey

Table A 2 Examples of minor food groups included in the major and sub-major food groups used in the Australian Health Survey.

Major food group	Sub-major food groups	Minor food groups and/or examples
Non-alcoholic beverages	Tea	Tea (caffeinated or decaffeinated); herbal tea
	Coffee and coffee substitutes	Coffee (caffeinated or decaffeinated), coffee substitutes
	Fruit and vegetable juices, and drinks	Fruit and vegetable juice (fresh of commercially prepared); fruit drinks
	Cordials	Made from concentrate (incl. artificially sweetened)
	Soft drinks, and flavoured mineral waters	Cola, non-cola and flavoured mineral waters (incl. intense sweetened)
	Other beverage flavourings and prepared beverages	Fortified and unfortified beverages flavourings (including prepared with water or milk); breakfast cereal beverages
Cereals and cereal products	Flours and other cereal grains and starches	Grains, rice and cereal flours and starches
	Regular breads, and bread rolls (plain/unfilled/untopped varieties)	Wheat based and non-wheat based breads (incl. gluten free)
	English-style muffins, flat breads, and savoury and sweet breads	Sweet (filled or unfilled) and savoury breads
	Pasta and pasta products (without sauce)	Wheat and non-wheat based pasta and noodles; filled pasta
	Breakfast cereals, ready to eat	Sweetened and unsweetened breakfast cereals (wheat based and non-wheat based)
	Breakfast cereals, hot porridge style	Porridge style (from oats or other cereals)
Cereal based products and dishes	Sweet biscuits	Plain, filled, coated, uncoated and all flavours sweet biscuits
	Savoury biscuits	Wheat-based and non-wheat based varieties
	Cakes, muffins, scones, cake-type desserts	Scones; cakes; cake mixes; cake-type desserts; slices; and other desserts containing cereals.
	Pastries	Filled or unfilled, sweet or savoury (incl. pies, rolls, quiches)
	Mixed dishes where cereal is the major	Pizza; sandwiches; burgers;

	ingredient	tortilla-based dishes; savoury pasta/noodles/rice dishes; dumplings; sushi
	Batter-based products	Pancakes; waffles; doughnuts
Fats and oils	Butters	Butter
	Dairy blends	Regular or reduced fat varieties
	Margarine and table spreads	Polyunsaturated, monounsaturated, cooking margarine (incl. with added phytosterols)
	Plant oils	Polyunsaturated, monounsaturated and blended varieties
Fish and seafood products and dishes	Fin fish (excluding commercially sterile)	Fresh or smoked (flathead, snapper, salmon)
	Crustacea and molluscs (excluding commercially sterile)	Prawn; octopus; scallop; squid
	Packed (commercially sterile) fish and seafood	Fish patty; canned fish (incl. flavoured)
	Fish and seafood products (homemade and takeaway)	All seafood battered or crumbed
	Mixed dishes with fish or seafood as the major component	
Fruit products and dishes	Pome fruit	Apples and pears
	Berry fruit	All berry fruits
	Citrus fruit	Orange; lemons; and other citrus fruits
	Stone fruit	Peaches; nectarines; and other stone fruits
	Tropical and subtropical fruit	Bananas; pineapple; and other tropical fruits
	Other fruit	Grapes
	Mixtures of two or more groups of fruit	Fresh or canned
	Dried fruit, preserved fruit	
Egg products and dishes	Eggs	Eggs (incl. fortified) from chicken or other
	Dishes where egg is the major ingredient	Sweet or savoury dishes (soufflé)
Meat, poultry and game products and dishes	Beef, sheep and pork, unprocessed	Beef; lamb; mutton; pork; veal
	Poultry and feathered game	Chicken and other poultry
	Sausages, frankfurts and saveloys	Sausages
	Processed meat	Bacon; ham; salami; dried meats
	Mixed dishes where beef, sheep, pork or mammalian game is the major component	Meat dishes with gravy, tomato-based sauce (incl. with added pasta or rice and/or vegetables); crumbed or battered or loaf meat dishes
	Mixed dishes where poultry or feathered game is the major component	Poultry dishes with gravy, tomato-based sauce (incl. with added pasta or rice and/or

		vegetables); crumbed or battered or loaf poultry dishes
Milk products and dishes	Dairy milk (cow, sheep and goat)	Full, reduced or non-fat milk; powdered, evaporated milk; and non-bovine milk
	Yoghurt	Flavoured or unflavoured yoghurt; yoghurt-based drinks
	Cream	Regular or increased fat; sour cream; cream substitutes
	Cheese	Hard, unripened (incl. cream and cottage cheese), ripened (incl. camembert, brie) and processed cheese
	Frozen milk products	Ice cream; frozen yoghurts
	Custards	
	Other dishes where milk or a milk product is the major component	Dairy desserts; and milk, cream or cheese-based desserts
	Flavoured milks and milkshakes	Coffee, fruit and other flavours milk-based drinks
Dairy and meat substitutes	Dairy milk substitutes, unflavoured	Soy-based, cereal-based and nut-based milk substitutes drinks
	Soy-based yoghurts	
Soup	Soup, homemade from basic ingredients	Vegetable only or with meats
	Canned condensed soup (unprepared)	Vegetable only or with meats
	Soup, commercially sterile, prepared from condensed or sold ready to heat	Vegetable only or with meats
Seed and nut products and dishes	Seeds and seed products	Sunflower seeds (raw, roasted, salted and unsalted)
	Nuts and nut products	Peanuts; coconuts
Savoury sauces and condiments	Gravies and savoury sauces	Gravy (prepared and dry), tomato-based and dairy-based sauces (homemade or commercial)
	Pickles, chutneys and relishes	Fruit or vegetable based pickles and chutneys
	Salad dressings	Mayonnaise; cream-style dressing; vinegar; French or Italian dressings
	Dips	Dairy-based, vegetable-based or legume-based
Vegetable products and dishes	Potatoes	
	Cabbage, cauliflower and similar brassica vegetables	
	Carrot and similar root vegetables	
	Leaf and stalk vegetables	Artichoke; asparagus, Incl. herbs and seaweed
	Peas and beans	Incl. sprouts
	Tomato and tomato products	
	Other fruiting vegetables	Pumpkin, squash, mushroom,

		sweetcorn
	Other vegetables and vegetable combinations	Incl. onion, leek, garlic
	Dishes where vegetable is the major component	Salads (with to without added meats/eggs); stuffed or fried vegetables
Legume and pulse products and dishes	Mature legumes and pulses	Bean (red kidney; broad) raw or cooked
	Mature legume and pulse products and dishes	Casserole dish with legumes and pulses
Snack foods	Potato snacks	Potato crisps
	Corn snacks	Corn chips and popcorn
	Other snacks	Extruded snacks (pappadam, noodle snacks)
Sugar products and dishes	Sugar, honey and syrups	
	Jam and lemon spreads, chocolate spreads, sauces	
	Dishes and products other than confectionery where sugar is the major component	Sugar-based desserts; gelato and sorbets; frosting
Confectionery and cereal/nut/fruit/seed bars	Chocolate and chocolate-based confectionery	Plain; with nuts and other fillings; carob-based
	Fruit, nut and seed-bars	
	Muesli or cereal style bars	With or without fruits; with or without fruit paste or yoghurt topping
	Other confectionery	Lollies (incl. intense sweetened); chewing gum
Alcoholic beverages	Beers	
	Wines	Red; white or fortified wines
	Spirits	
	Cider and perry	
Special dietary foods	Formula dietary foods	Meal replacement; sports protein powders; supplementary and medical beverages (dry or prepared)
Miscellaneous	Yeast, and yeast vegetable or meat extracts	Vegemite

Appendix IX Average daily intake of major food groups

Table A 3 Average daily weights of major food groups (ordered by weight) consumed by men with prostate cancer in comparison with elderly men from the Australian Health Survey.

	Weight consumed by men with prostate cancer (g/day)	Weight consumed by elderly Australian men (g/day)	P values
Non-alcoholic beverages	875 (0 - 2557)	1250	0.003
Vegetable products and dishes	303 (73 - 553)	175	< 0.001
Milk products and dishes	225 (0 -841)	203	0.49
Fruit products and dishes	215 (0 - 848)	214	0.23
Cereals and cereal products	151 (30 - 321)	140	0.20
Alcoholic beverages	107 (0 - 1997)	379	< 0.001
Meat, poultry and game products and dishes	106 (2 - 22)	150	0.007
Cereal based products and dishes	47 (0 - 37)	105	0.002
Fish and seafood products and dishes	23 (0 – 129)	130	< 0.001
Egg products and dishes	19 (0 - 102)	88	< 0.001
Savoury sauces and condiments	19 (0 - 89)	21	0.80
Confectionery and cereal/nut/fruit/seed bars	6 (0 - 124)	23	0.002
Fats and oils	5 (0 - 85)	10	0.002
Seed and nut products and dishes	4 (0 - 164)	26	0.009
Sugar products and dishes	1 (0 - 120)	17	< 0.001
Dairy & meat substitutes	0 (0 - 534)	155	< 0.001
Soup	0 (0 - 145)	309	< 0.001
Legume and pulse products and dishes	0 (0 - 100)	161	< 0.001
Snack foods	0 (0 - 57)	18	< 0.001
Special dietary foods	0 (0 - 14)	-	-
Miscellaneous	< 1 (0 - 29)	< 1	0.52

Weight of food group consumed by men with prostate cancer presented as median (range), and for elderly Australian men presented as median.